ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 31 (O.S., Vol. XXXV) DECEMBER, 1949 NUMBER 6

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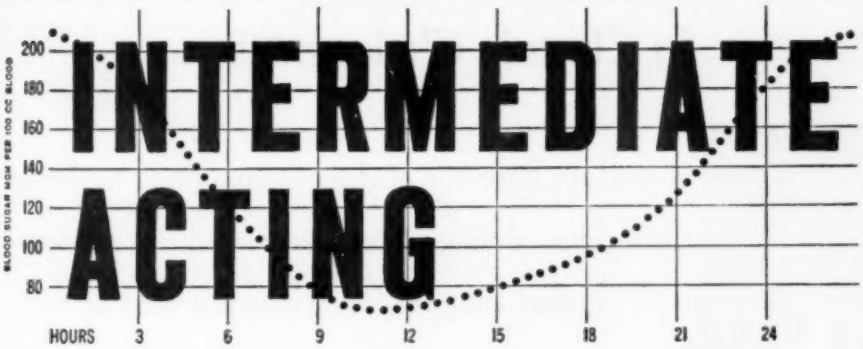
Subscription per volume or per annum, net postpaid, $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1938.



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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
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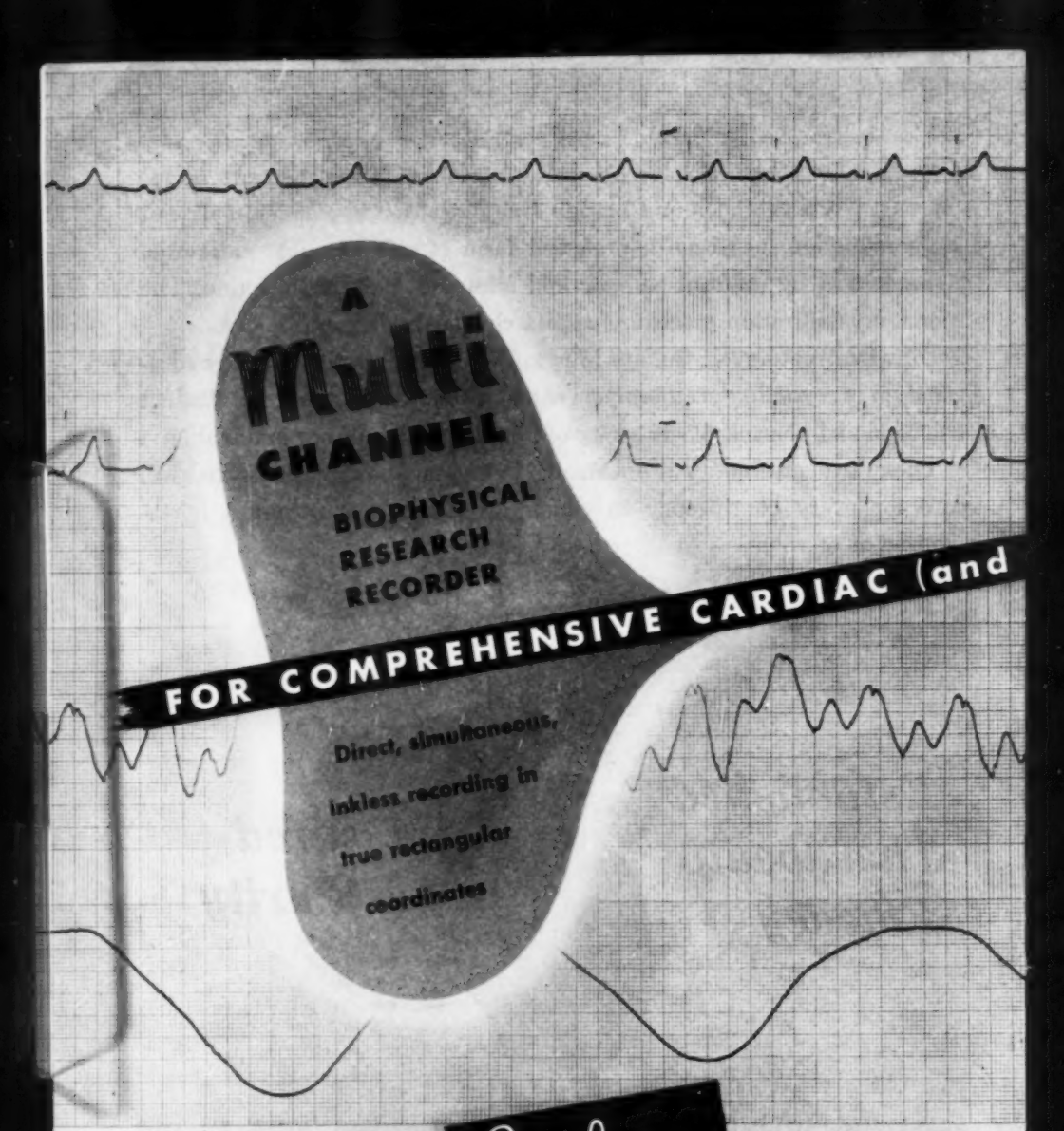

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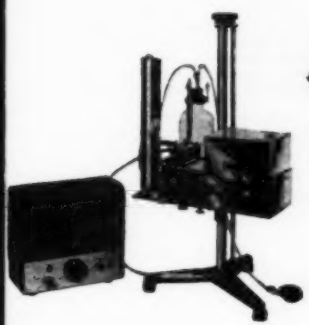

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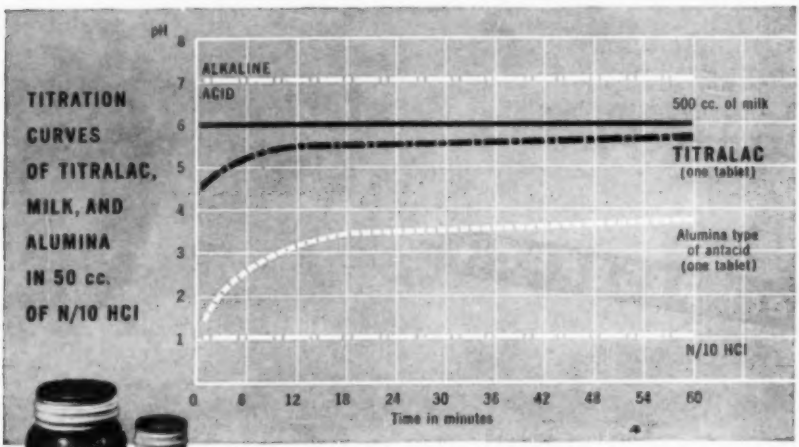

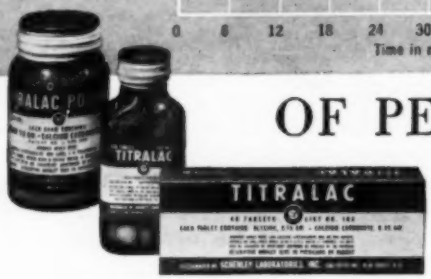

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REFERENCES

1. Rossett, N. E., and Flexner, J.: Ann. Int. Med. 18: 193 (1944). 2. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: Guy's Hosp. Reports 78: 191 (1928). 3. Aaron, A. H.; Lipp, W. F., and Milch, E.: J. A. M. A. 139: 514 (Feb. 19) 1949. 4. Kirsner, J. B., and Palmer, W. L.: Illinois M. J. 94: 357 (Dec.) 1948. 5. Kimball, S.: in Practice of Medicine (Tice). Hagerstown, Md., W. F. Prior Company, Inc., 1948; p. 210. 6. Special Article: M. Times 76: 10 (Jan.) 1948.

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ANNALS OF
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THE ETIOLOGY AND MANAGEMENT OF THE HEMORRHAGIC DIATHESES *

By CHARLES A. DOAN, M.D., F.A.C.P., *Columbus, Ohio*

HEMORRHAGE uncontrollable except by expert medical management, may present in the practice of any physician at any time. Under normal conditions, the integrity of the vascular system and the circulating fluidity of the blood reflect a nice physiologic balance in an exceedingly sensitive and complicated coagulation mechanism. The physical-chemical intricacies of normal blood coagulation continue to challenge the best thought of many investigators and to stimulate ever more detailed experimentation in many laboratories, in the attempt to better understand and to more effectively solve the clinical problems centering about abnormal hemorrhage. The concepts and terminology arising from parallel efforts in different laboratories have resulted in much confusion among clinical diagnosticians regarding the interrelationships of the basic coagulation phenomena themselves. The first prerequisite, therefore, in approaching this field is a definition of terms, currently presumed to be interchangeable, as they have been coined to describe the observed sequence of events in normal blood coagulation (Graph A, page 981—modified after Quick) the exact chemical factors concerned having not yet been isolated.

It is now agreed that both platelets and plasma factors are essential for completely physiologic blood coagulation, Brinkhous and Conley each having demonstrated the lack of spontaneous coagulation of blood plasma for long periods when blood is carefully collected in silicone (methylchlorosilane) coated tubes, the blood platelets being promptly separated and the plasma stored at low temperatures (4° C). Quick has hypothesized the liberation of an enzyme, thromboplastinogenase, from disintegrated platelets, which is essential for the conversion of plasma thromboplastinogen to thromboplastin (thrombokinase). Injured tissue may also be the source of thrombo-

* Presented as a Morning Lecture at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948. Received for publication September 8, 1949.

plastin. It is believed that the platelets release a second enzyme which promotes vasoconstriction of the local capillary bed as an aid in prompt coagulation. The plasma thromboplastinogen of Quick is identical with the antihemophilic globulin of Fraction I of Cohn, as extensively studied by Taylor and associates.

Prothrombin (a large molecular glycoprotein) is thought to be present in plasma in both a free and combined form (prothrombinogen) and it is suggested in the chart by the broken line that plasmin may be one of the accelerators of the production of free prothrombin from prothrombinogen. The reaction between thromboplastin and prothrombin has been shown to be stoichiometric, therefore the consumption of prothrombin may be measured in any given coagulation reaction and is directly proportional to the amount of thromboplastin available, which in turn is a function of the available platelets. Dicumarol's anticoagulant effect is mediated through a lowering of the plasma prothrombin level. Ionized calcium is a catalytic essential in this second phase of blood coagulation and it is by the inactivation of these ions that sodium citrate or calcium oxalate prolong the fluidity of shed blood.

Seegers and associates have noted that mixtures of purified prothrombin, thromboplastin and calcium ion produce only 30 to 40 per cent yield of thrombin in one to one and one-half hours, whereas, when plasma previously activated with thrombin is added, the period of slow thrombin production is reduced to about two minutes and the yield is 100 per cent. They attribute this to the presence of an accelerator globulin, Ac-globulin, inert in plasma but promptly converted to active catalytic serum Ac-globulin in the presence of thrombin. It now seems probable that Seegers' Ac-globulin is identical with Quick's prothrombin A (the latter's prothrombin B being true prothrombin). Owren's factors V and VI are closely identified with, if not actually, Seegers' Ac-globulin and Quick's prothrombin A, in accomplishing the second phase of coagulation.

The third phase in blood coagulation remains unchanged from earlier concepts in that thrombin interacts with the plasma fibrinogen to form the fibrin clot. It is at this point that heparin inhibits prothrombin conversion and the thrombin-fibrinogen reaction and thereby prolongs blood coagulation. Retraction of the clot in time and degree is directly proportional to the excess of platelets which may be present; as the number of platelets is diminished the speed of prothrombin consumption is decreased, and below a critical level, which varies in different patients, a serious defect in coagulation is present, though masked by a normal coagulation time (Quick). Thrombin, itself, has a "labilizing influence" on the blood platelets, so that with the first thrombin formed in a given coagulation system, there is an acceleration in the speed of release of thromboplastinogenase with more rapid clot formation in the presence of an adequate supply of platelets.

Fibrinolysis, the dissolution of blood clots, is exceedingly important from a clinical standpoint. It is now established that there is present in normal plasma an inactive precursor of plasmin termed plasminogen. Plasmin is

a synonym for the proteolytic enzyme activity which has been known variously as serum trypsin, serum tryptase, serum protease, fibrinolysin and thrombolysin. The streptococcic filtrate factor comparable in action on plasminogen or plasmogen has been called streptokinase, and the antibody-like resistance which may be demonstrated in certain patients recovered from streptococcic infections has been designated antistreptokinase. In the albumin fraction of plasma has been found an inhibiting enzyme, antiplasmin (Macfarlane).

Obviously a clinical bleeding tendency may occur under a wide variety of pathologic circumstances, and be influenced by one or more of many potential factors acting at any one of the many points in the complex mechanism of blood coagulation. The first clinical sign may appear and re-appear as an asymptomatic transitory purpuric manifestation, apparently limited to skin or mucous membranes, or the syndrome may present as one of the most acute, fulminant and critical emergencies with which the physician is ever called upon to deal. The specificity, and therefore the success of the therapeutic regimen advised, is directly dependent upon the preciseness and exactitude, and, in the acute purpuras, the promptness of the differential etiologic diagnosis in any given patient.

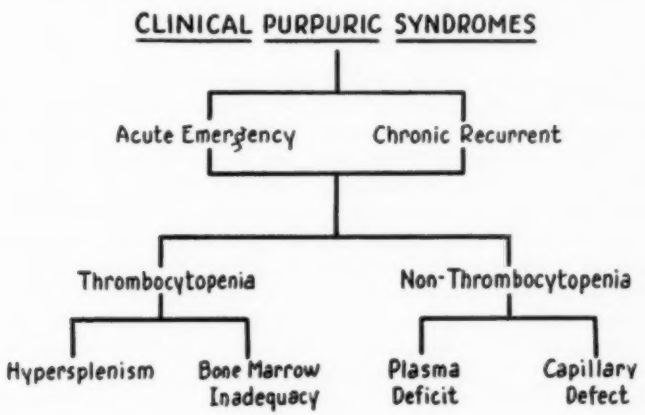

FIG. 1.

The approach to an understanding of the particular mechanism involved can best be made systematically, keeping in mind certain rather broad principles which underlie the hemorrhagic diatheses (figure 1). When a true purpuric extravasation of blood has been identified by its color, character and permanence, or if persistent bleeding occurs other than in the skin, it at once becomes essential to know whether the thrombocytes are normal or are decreased in the peripheral circulation.

Thrombocytopenic Purpura

If and when few or no blood platelets are to be found in the circulating blood of any patient with clinical purpura, a study of the bone marrow is essential to determine whether this deficit is secondary to (1) a relative or absolute central (bone marrow) megakaryocytic inadequacy, or, (2) an excessive peripheral (splenic) demand (figure 2).

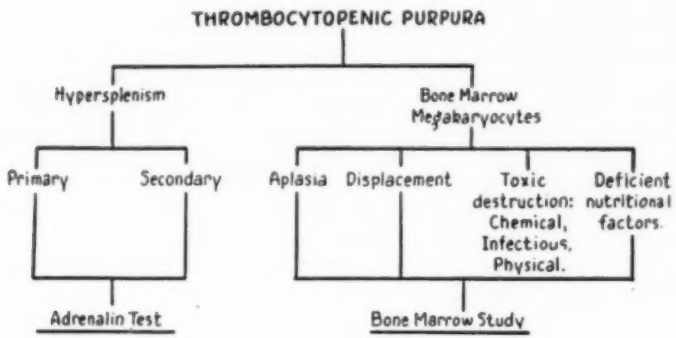

Fig. 2.

Thrombocytopenic purpura due to *defective bone marrow.*

Primary Marrow Aplasia. Generalized purpura is frequently the first sign of progressive marrow hypoplasia. When, upon repeated bone marrow studies, obtained from the manubrium and the body of the sternum, from selected spinous processes and from the crest of the ileum, no megakaryocytes are found, plus definite evidence of a beginning marrow pancytopenia,—and when neither past personal history nor direct investigation reveals toxic environmental, medicinal or bacterial factors, primary hypoplasia with or without an osteofibrosis or osteopetrosis mechanism may be established. In a certain proportion of such patients extra-medullary hematopoiesis in spleen and liver may partially compensate for the marrow hypoplasia. Do not misinterpret the significance of splenomegaly in these cases, even when evidence of periodic hypersplenism is obtained. In the early stages, with only moderate marrow hypoplasia and in the proved absence of ectopic splenic hematopoiesis, splenectomy, in carefully selected patients, may be followed by a remission of months or years.

Supportive replacement of fresh citrated blood transfusions (not "bank blood" more than 24 hours old), selected, typed and carefully matched, is the treatment of choice. Polycythemic donors, in our experience, have made particularly effective blood contributions to such patients, inducing in some instances more prolonged remissions than have normal donors (figure 3). Though such has never happened to our knowledge, if the transmission of a

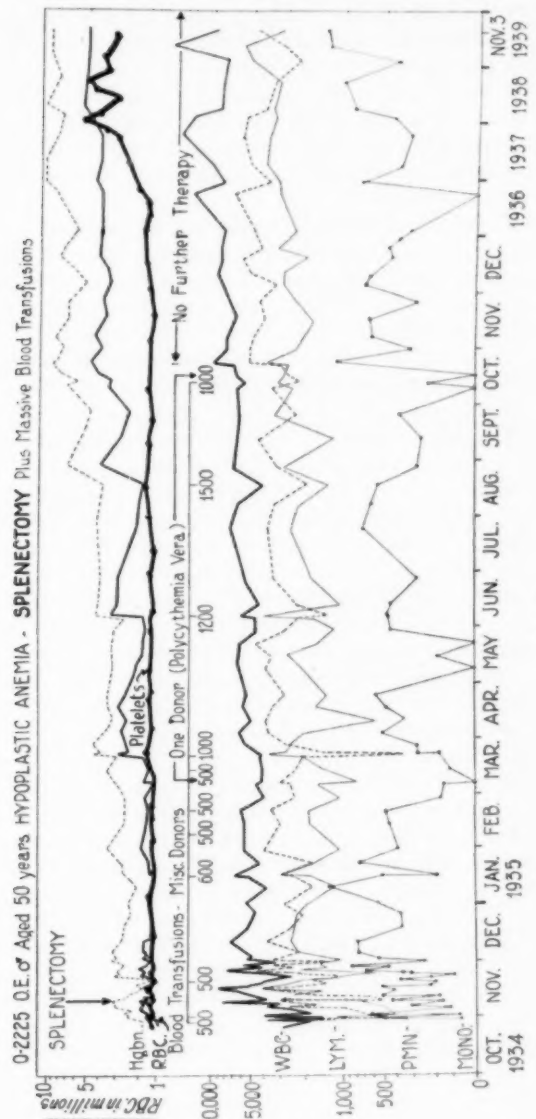
0-2225 O.E. ♂ Aged 50 years HYPOPLASTIC ANEMIA - SPLENECTOMY Plus Massive Blood Transfusions
SPLENECTOMY
Platelets
Hgbn.
RBC.
Blood Transfusions - Misc. Donors
One Donor (Polycythemia Vera)
No Further Therapy
Platelets in Thousands
Hgbn. in grams
RBC. in millions
WBC.
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FIG. 3.

pan-marrow hyperplasia to patients with a primary marrow aplasia could be accomplished, it should lead to a longer and more readily controlled life than now is possible in progressive aplastic anemia.

The generous use of any or all of the presently known stimulatory and maturing factors for blood cells—liver, folic acid, vitamin B^{12} et al.,—have, thus far, failed to affect marrow regeneration in this type of patient, though theoretically and experimentally nutritional deficiency does at times result in progressive marrow hypoplasia.

Nutritional Deficiency Marrow Hypoplasia. In addition to the now well-known vitamin components from the B and C complexes, the E.M.F. from liver extract, and the trace mineral catalysts, copper and cobalt, it is recognized that certain amino acids are also essential to optimum hematopoiesis. Under certain naturally occurring circumstances, in individuals with food idiosyncrasies, or gastrointestinal abnormalities concerned with disturbed digestion and absorption, thrombocytopenic purpura on a deficiency basis secondary to general marrow hypoplasia, may occur. The correction of any specific deficiency will be followed by the regeneration of megakaryocytes and the disappearance of all purpuric manifestations.

Toxic marrow destruction or inhibition may result from industrial chemicals (see benzol, figure 4), therapeutic drugs (see Sedormid, figure 5), physical agents, roentgen-ray and radioactivity, virus and bacterial infections. Careful supravital study of the fresh living marrow in thrombocytopenic purpura will at once reveal clearly and unequivocally any specific damage to the megakaryocytes which may be responsible for the circulating platelet deficit. Vacuolated nuclei and cytoplasm with chromatin karyorrhexis and increased phagocytosis of specific cellular debris are unmistakable evidences of such toxic damage. The case history and other pertinent data will establish the specific antigenic or direct toxic agent in each instance. Immediate removal or discontinuance and elimination of the offending agent, accompanied by supportive fresh blood transfusions containing viable platelets, will permit the regeneration of megakaryocytes and thrombocytogenesis in a time relationship proportional to the severity and duration of the toxic influence. If complete recovery does not result, splenectomy in selected instances is followed by marrow recompensation (figure 4).

In infections, clinical purpura may be due to central marrow toxemia as just described, or to bacterial emboli, or to capillary endothelial damage. Intensive specific chemo- or antibiotic therapy, 200 to 500 mg. vitamin C daily, frequent (q. 8 hrs.) small (200 c.c.) fresh blood transfusions, with 24 hour supportive nursing care, will usually result in recovery.

Myelophthisic (Displacement) Thrombocytopenia. The bone marrow study in some patients with thrombocytopenic purpura will reveal the first evidence of foreign cell invasion at the expense of megakaryocytes and eventually of the other normal marrow elements. Therapy is dependent upon the type and character of the cellular hyperplasia. The various leukemic states, more particularly acute monocytic leukemia and leuko-lympho-

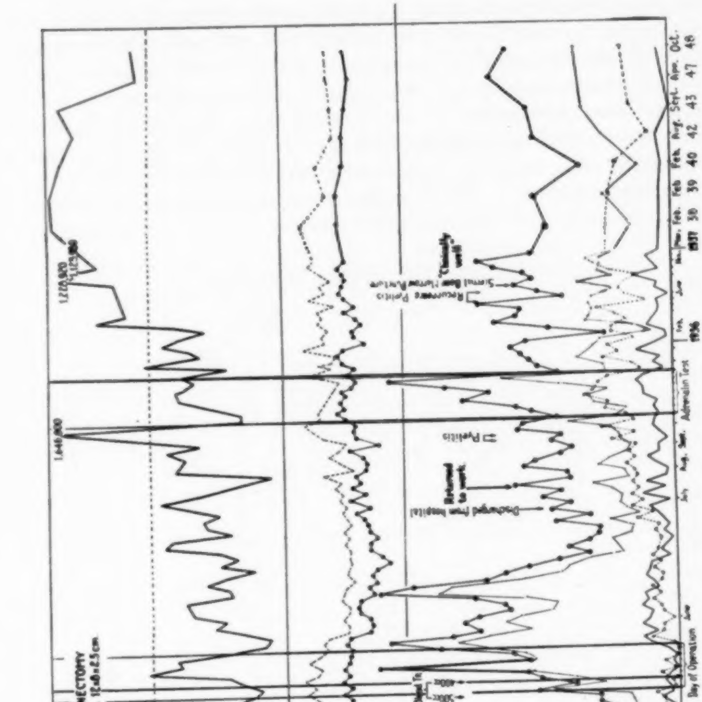
PLATELETS
R.B.C.
W.B.C.
SPLENECTOMY
"Normal" Mean for Platelets
Day of Operation
Adrenalin Test

FIG. 4.

sarcoma (acute lymphatic leukemia) may be ushered in with a clinical purpuric syndrome. Fresh blood transfusions and antibiotic chemo-therapy are indicated initially, until the more or less specific anti-leukemic agents (the nitrogen mustards, folic acid antagonists, urethane) now available have had the time interval required to inhibit and destroy the displacing cellular units and permit normal hematopoietic regeneration. Multiple myeloma, osteo-Hodgkin's and metastatic carcinoma may be clinically initiated by thrombocytopenic purpura. The specific treatment of such purpuras, *due to marrow involvement* is the fundamental treatment of the principal disease.

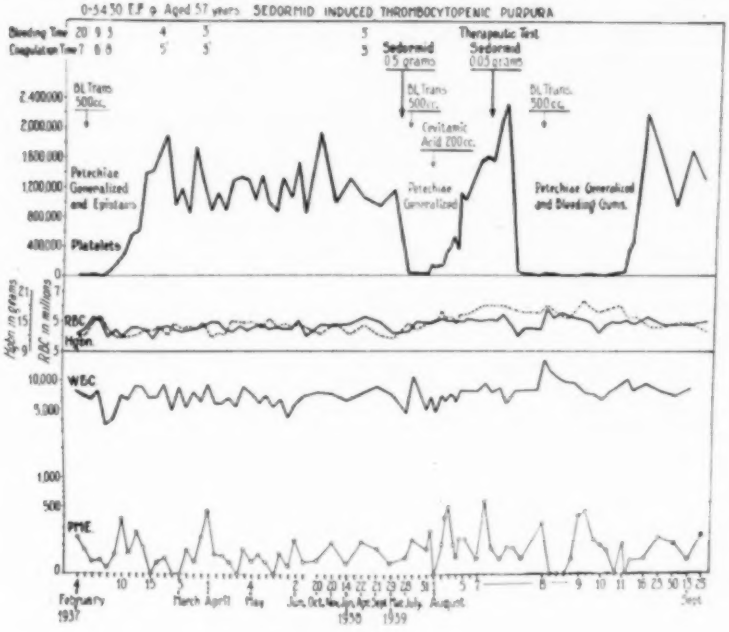

FIG. 5.

Thrombocytopenic Purpura Hemorrhagica—Hypersplenism. When peripheral thrombocytopenia has been found associated with clinical purpura and the bone marrow studies not only have failed to reveal any evidence of cellular aplasia, displacement, damage, or toxicity, but actually reflect an excessive multiplication of megakaryocytes in all stages of immaturity,—the more mature units showing active cytoplasmic platelet fragmentation in the living supravital preparations,—the conclusion is justified that despite the apparently uninhibited compensatory megakaryocytic hyperplasia, the peripheral platelet demand is in excess of the available supply. When the spleen

is *not* demonstrably enlarged, ***primary splenic thrombocytopenic purpura*** is the most likely diagnosis.

Primary Hypersplenic Thrombocytopenic Purpura (Werlhof's Disease). In the absence of any other demonstrable pathologic mechanism, specifically bone marrow damage or inadequacy, the adrenalin test may reveal an hypersequestration of platelets by a normal sized spleen indicative of a primary specific withdrawal or inhibition of circulating platelets (figure 6). Note that the postsplenectomy adrenalin test failed to reveal the hypersequestration

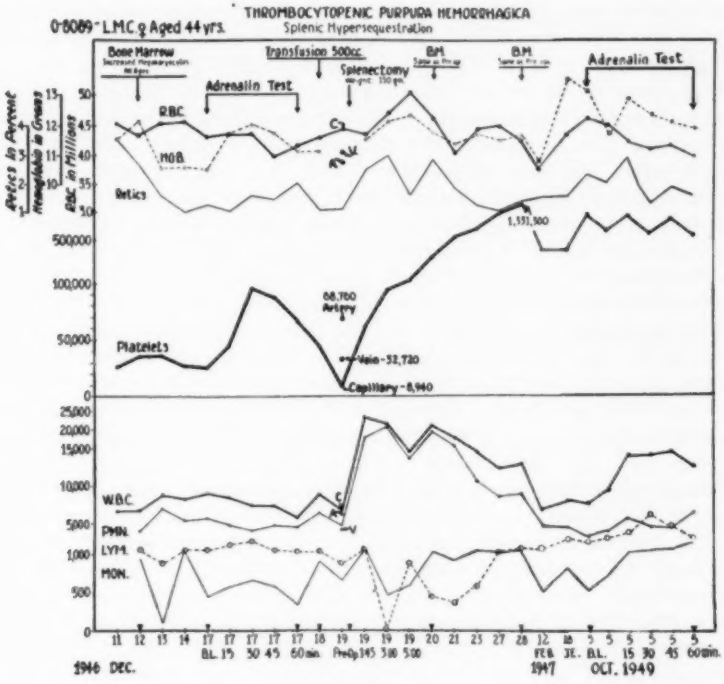

FIG. 6.

of thrombocytes, so well demonstrated during the purpuric episode. The clinical manifestations may be relatively benign, chronically recurring, chiefly cosmetic in the showering of skin petechiae, *or* they may develop suddenly and involve multiple critical hemorrhages involving mucous membranes of nose and mouth, gastrointestinal tract, genito-urinary system, uterus, and central nervous system. In the acute episode there may be time only for peripheral blood and bone marrow diagnostic studies. When there is severe headache, stupor, or other signs of increased pressure due to intracranial

hemorrhage, careful decompression via spinal puncture should be promptly accomplished. Multiple emergency *fresh* blood transfusions may be necessary to replace acute blood loss and prevent imminent shock, as well as to supply platelets in the attempt to control further blood loss.

Whether the syndrome is chronic *or* acute, splenectomy is the only effective therapeutic procedure for this mechanism. A particularly careful search for accessory splenic tissue should be made at the first surgical exploration—including a liver biopsy and a mesenteric lymph node specimen for immediate histologic study and future reference. An hypersplenic relapse may be precipitated by as little as 5 grams of splenic tissue in patients having this trait (figure 7). When faced with such a clinical and hematologic recurrence, it is entirely justifiable to attempt to locate aberrant splenic tissue by thorotrast visualization. Once again surgical removal is the only known effective therapy. When a generalized hyperplasia of hyperfunctioning reticulo-endothelial cell phagocytes occurs in the liver and lymph nodes, complete surgical excision is obviously impossible and conservative measures, chiefly serial blood transfusions are at the present time the only treatment. Irradiation, vitamins, snake venom, parathormone, calcium, rutin, have all proved ineffective in this clinic, in this type of case.

Secondary Hypersplenic Thrombocytopenic Purpura. When there is an obvious enlargement of the spleen with adrenalin test evidence of specific platelet hypersequestration, and the bone marrow shows only compensatory megakaryocytosis without myelophthisic or toxic marrow damage, a hypersplenic syndrome secondary to some other disseminated constitutional disease must be considered. Primary splenic Hodgkin's granuloma, splenic Gaucher's disease, chronic leukemic involvement of the splenic parenchyma by any cell type, tuberculosis or tertiary lues of the spleen, congestive splenomegaly secondary to myocardial decompensation, acute splenic tumor of infectious etiology,—all have been observed to be associated on occasion with a more or less acute hypersplenic thrombocytopenic purpura in which the bone marrow may be excluded as a contributing factor. Under such circumstances emergency splenectomy should be performed on exactly the same reasoning as for primary hypersplenism, irrespective of the known presence elsewhere in the body of a serious disease process. The immediate danger without surgery is fatal hemorrhage; the more remote danger of progressive constitutional disease may better be met by whatever specific therapy is available after the hypersplenic complication has been permanently eliminated. With modern anesthesia and expert surgical technic, the risk of surgery in these patients is far less than the dangers of spontaneous fatal hemorrhage or of a surgically induced exacerbation of the basic disease process. One successful facing of such a crisis will convince the doubtful of the rationale here advocated.

An obese white male patient presented with an acute purpuric syndrome. Initial studies showed an absolute peripheral thrombocytopenia and a typical bone marrow with compensatory megakaryocytic hyperplasia as the only cellular abnormality

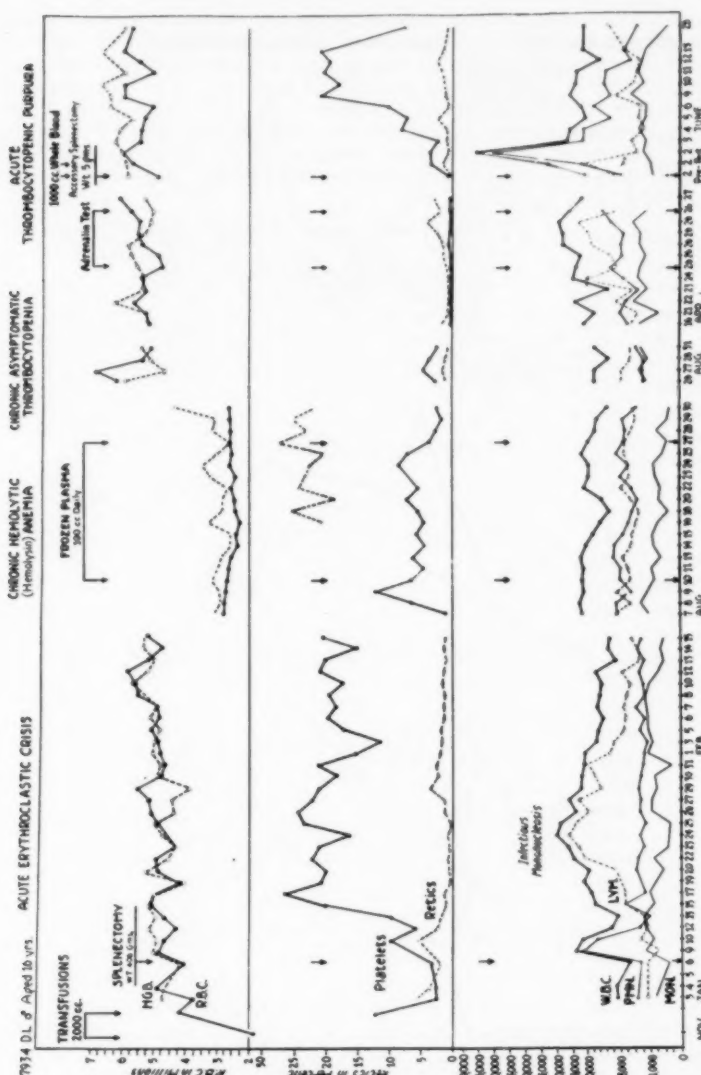
O-7934 DL. ♂ Aged 16 yrs.
ACUTE ERYTHROCLASTIC CRISIS
CHRONIC HEMOLYTIC (Hemolysin) ANEMIA
CHRONIC ASYMPTOMATIC THROMBOCYTOPENIA
ACUTE THROMBOCYTOPENIC PURPURA
TRANSFUSIONS 1000 cc.
SPLENECTOMY
FROZEN PLASMA
Adrenalin Test
Hemoglobin in Grams
R.B.C. in Millions
Platelets
Reticulocytes
Platelets
Retics
W.B.C.
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FIG. 7.

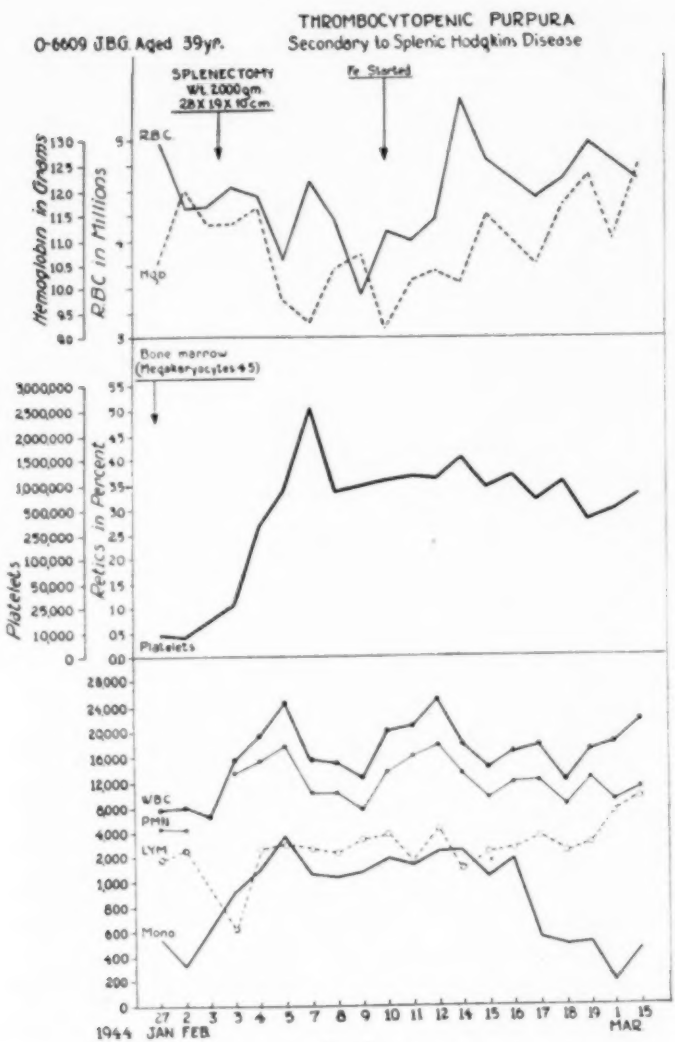


FIG. 8.

(figure 8). Neither spleen nor liver could be palpated and all plasma coagulation factors and routine blood chemistry studies were found to be within physiologic limits. A diagnosis of primary splenic thrombocytopenic purpura was made and immediate surgery advised. Supported by fresh whole blood transfusions, an emergency surgical exploration was accomplished. An enlarged spleen was found and removed.

without evidence of liver or lymph node involvement. On supravital and fixed section study the pathology of Hodgkin's granuloma was revealed, apparently primary in the spleen. The specificity of the hypersequestration of platelets by this Hodgkin's involved spleen was proved by the dramatic and immediate rise in circulating platelets with improved blood coagulation, which was evident during the completion of the operation. Though unsuccessful in removing the sole focus of Hodgkin's, as we had hoped, other manifestations of the disease developing during the ensuing 18 months —there was never any recurrence of the thrombocytopenia or purpuric complications.

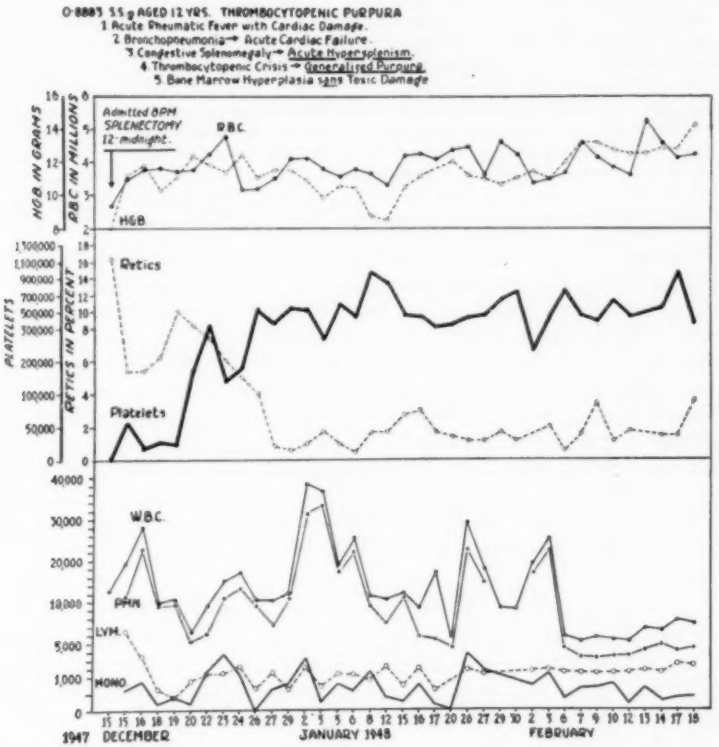


FIG. 9.

A young girl, aged 12 years, was admitted to the University Hospital as an acute emergency with generalized purpura, persistent epistaxis and gastrointestinal and genito-urinary hemorrhages of three days' duration (figure 9). Repeated fresh whole blood transfusions, prior to admission, had failed to control the hemorrhagic diathesis even temporarily. An acute upper respiratory infection with bilateral pneumonitis had preceded the bleeding manifestations and a toxic etiology, bacterial or chemotherapeutic in origin was suspected. Peripheral blood studies confirmed the complete absence of circulating platelets, and a coincidental supravital survey of the bone-

marrow showed a pan-marrow hyperplasia, without any evidence of toxic cellular destruction or inhibition. The megakaryocytes were particularly observed to be multiplying and maturing and fragmenting their cytoplasm into platelets at a greatly accelerated tempo. Examination of the chest confirmed the existence of pneumonic involvement; the heart was greatly enlarged with systolic and diastolic mitral murmurs; both spleen and liver were enlarged and tender to palpation; and there was pedal, facial and sacral edema.

A history of acute rheumatic fever explained the mitral lesion and provided a plausible explanation for the evidence of cardiac decompensation. There was no family history of any hematologic dyscrasia. A tentative diagnosis of acute splenic, thrombocytopenic purpura was made, the sequence of events probably being acute rheumatic fever with residual cardiac damage, plus superimposed bilateral pulmonary infection with acute congestion and hemostasis in an unstable spleen as the heart began to fail. The patient was in extremis. Fresh whole blood transfusions were started simultaneously in two extremities and within four hours of her hospital admission, the spleen had been removed and normal coagulation reëstablished with plenty of platelets demonstrable in the circulation. The clinical improvement was equally dramatic even before chemo- and antibiotic therapy had had the opportunity to control fully the pulmonary and renal infections and digitalization the cardiac edema. Recovery was uneventful and has continued to the present time.

Prophylactic splenectomy should be advised and undertaken whenever a hypersplenic syndrome has been observed, either as a chronic or as an acute episode, even though one or more spontaneous remissions have intervened. The spleen is, at best, an unstable reservoir for platelets and for all of the other normal circulating blood cell elements and once it has been caught in any pathological hyperactivity, it is never again to be fully trusted. Sudden acute hemoclastic crises will usually recur, sooner or later, either spontaneously or precipitated by minor illnesses or accidents. Since the spleen is not essential to either normal human health or longevity, there are no known contraindications to its removal at any age. Chronic invalidism and acute fatalities are, on the other hand, more frequently the result of a pathologic spleen than has heretofore been generally realized.

Non-Thrombocytopenic Purpura

If and when normal or excessive numbers of qualitatively normal platelets are to be found in the circulating blood of any patient with clinical purpura immediate studies are indicated to differentiate between (1) specific plasma and/or (2) specific capillary defects (figure 10).

Plasma Coagulation Defects. The humoral or chemical factors initiating and inhibiting blood coagulation continue to present a most complex problem even to the expert investigators in this field. While tremendous progress has been made in the understanding and control of this vital series of coagulation phenomena the final chapter has not yet been written and, therefore, the complete control of all purpuric syndromes has not been attained (Graph A).

Hypoprothrombinemia. It is now routine to determine the prothrombin plasma level in every patient showing any hemorrhagic tendency and to maintain it at high normal levels, if possible, irrespective of the rôle which may be

played by other mechanisms. Low prothrombin levels have been shown to be responsible for purpura in "melena neonatorum" or "hemorrhagic disease of the newborn" (as low as 5 per cent of normal adult level); in obstructive jaundice, the absence of bile from the intestinal tract interfering with optimum absorption of the fat-soluble vitamin K; in liver disease sufficiently severe to interfere with its important function of prothrombinogenesis from vitamin K; in individuals on a low vitamin K diet; and in patients with hyperperistalsis or other intestinal pathology preventing proper vitamin K absorption.

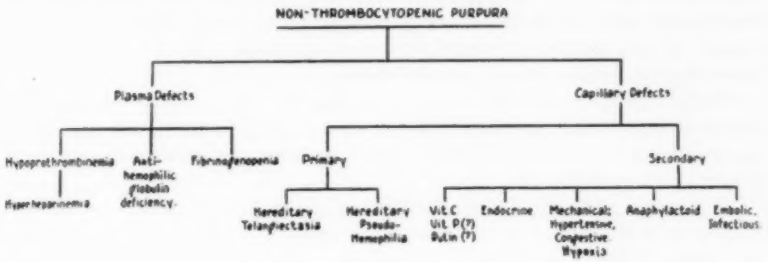
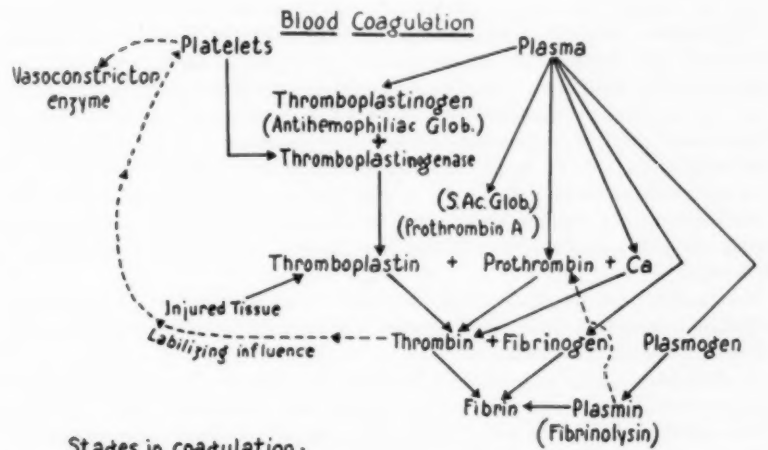


FIG. 10.



Stages in coagulation.

1. Thromboplastinogen + platelet enzyme → thromboplastin
2. Prothrombin + thromboplastin + Ca = thrombin
3. Fibrinogen + thrombin → fibrin

Modified after Quick

GRAPH A.

Synthetic derivatives of quinone have largely replaced the earlier concentrates of alfalfa extract and may be administered by any route, the dosage and strength of the various preparations being easily adjusted to the age of the patient and the severity of the hypoprothrombinemia. The water-soluble compound 4-amino-2-methyl-1-naphthol may be given to newborn infants in 1 mg. doses either intramuscularly or intravenously and repeated at six hour intervals until the symptoms are controlled. The water-insoluble 2-methyl-1,4 naphthoquinone is the most active preparation and may be given by mouth 2 to 5 mg. daily with bile salts or intramuscularly 2-4 mg. daily. Menadione, U.S.P., 2-methyl-naphthoquinone, has a daily oral dose of 1 mg. Only in the presence of extensive liver damage will this medication fail to restore the prothrombin promptly to normal levels and thus control the hemorrhagic diathesis due to this deficiency.

Small repeated fresh blood transfusions may be used to supply prothrombin directly in the newborn, and somewhat less effectively in adults. The prothrombin supplementing capacity of human blood decreases rapidly during blood bank storage.

Hyperheparinemia. Spontaneous coagulation of the blood within the circulation is prevented by the presence of heparin in physiologic concentration, acting through an inhibition of prothrombin conversion and the thrombin-fibrinogen reaction. Allen and associates have recently attributed prolonged bleeding following extensive irradiation and following the administration of cytotoxic drugs, such as the nitrogen mustards, to the presence of an excess of heparin or heparin-like substances, in addition to the thrombocytopenia which develops. Appropriate tests must be made whenever this mechanism is suspected. Protamine and toluidine blue dye have been more or less effective in controlling the hemorrhagic phenomena due to the hyperheparinemia. The recommended dosage of protamine is 0.5 to 2.0 mg. per kg. body weight, in 50 to 75 c.c. NaCl intravenously, each 24 hours, though toxic reactions may follow its administration in some patients. The toluidine blue dye is prepared and administered similarly, 1 to 4 mg. per kg. body weight. It may be repeated for several days and is usually well tolerated.

The thrombocytopenic components in this radiation-induced hemorrhagic diathesis must be supplied by repeated *fresh* whole blood transfusions until the marrow has recovered.

Anti-Hemophilic Globulin Deficiency. Ordinarily it is not difficult to recognize the male victim of a hemophilic heritage but frequently the differential diagnosis between a chronically recurring thrombocytopenic purpura and a mild, but true, hemophiliac requires considerable investigation, thought and observation. The wide difference in rationale of treatment in these two hemorrhagic diseases obviously demands precise diagnosis.

When the objective establishment of a recurring, if not constantly demonstrable, abnormally prolonged coagulation time, without thrombocytopenia has given circumstantial evidence of a "globulin defect" prophylactic therapy

may be necessary for the prevention of spontaneous hemorrhages in the normal course of living, and preceding elective surgery; *or* in the presence of trauma or emergency surgery rigid temporary control of the coagulation time may be mandatory, even life-saving.

Fresh whole blood, fresh plasma, or freshly frozen or lyophilized plasma obtained from "normal" donors, contains antihemophilic globulin, which will reduce the prolonged in vitro coagulation time of the blood from a hemophilic patient more or less to normal at once and for a variable period of time. The amount required and the frequency of readministration depend upon so many uncontrollable variables that only regularly repeated coagulation tests on carefully obtained samples of venous blood may determine these data for each individual patient, especially in times of critical need.

Plasma Fraction I of Cohn contains the largest increment of anti-hemophilic globulin, and may be used entirely effectively. It is available through the National American Red Cross. Again, however, no standard dosage can be recommended, (1) because of the variability of the potency of each lot prepared; (2) because of the variability in the hemophilic patient's own need from time to time; and (3) because of the greater antigenicity of Fraction I than whole blood.

Unless the very occasional patient should develop a specific "antibody-like" resistance to transfused normal human globulin, the sources of anti-hemophilic globulin, including fresh normal whole blood or human plasma are now such as to make possible the approach to this problem today with some equanimity and a greater assurance of success. In the more acutely susceptible individuals a regimen of regular prophylactic supplements of antihemophilic globulin-containing plasma may be established on a one to three day basis with some promise of success.

Fibrinogenopenia. The normal human plasma fibrinogen level ranges from 0.2 to 0.4 gm. per cent. Afibrinogenemia occurs rarely as a congenital and usually as a familial disease with the hemorrhagic tendency becoming apparent, and therefore, dangerous, only secondary to trauma. Fresh blood or plasma transfusions may be effectively used to supply the fibrinogen deficit.

Fraction I of Cohn contains the fibrinogen portion of the plasma and Diamond has reported its successful use as a prophylactic in the satisfactory control of patients with this defect when given regularly, for example in one of his patients, every three days. Each patient must, of course, be studied individually for dosage and frequency.

Capillary Defects Resulting in Clinical Purpura.

Primary Hemorrhagic Telangiectasia. Hereditary telangiectasis is a rather common, usually benign, hereditary abnormality, its pin-head sized or larger nodular vascular tumors and spider angiomata being more frequently of cosmetic than hemorrhagic concern. The bright red compressible capillary tufts in skin and mucous membranes have often been mistaken for the petechiae of true purpura on superficial examination. There is, however, no

thrombocytopenia and no demonstrable plasma coagulation defect, but only dilated capillary and venous sinusoidal fragility, responsible for the spontaneous hemorrhages which occur with increasing frequency with age, and which may cause chronic invalidism or even threaten life, itself, at times.

Obliterative cauterization of particularly susceptible localized tufts in the mucous membranes of nose and throat is the treatment of choice. High vitamin C and adequate vitamin K are essential prophylactic supplements. Blood transfusion is an emergency supportive measure, as in all hemorrhage.

Hereditary Pseudohemophilia. We place this bisexually-occurring, hereditary, hemorrhagic dyscrasia under the category of "primary capillary defect" since no qualitative or quantitative thrombocyte and no plasma coagulation defects have been discovered to account for the severe and sometimes fatal hemorrhages. No obvious hemangiomata occur, but Macfarlane of Oxford, England, has demonstrated the apparently inherent inability of the capillary wall in these patients to contract following injury. This mechanism leads to that very rare phenomenon of a ***prolonged bleeding time*** in a patient with non-thrombocytopenic purpura. Fresh whole blood transfusions give the best results and usually suffice though they do not alter either the normal coagulation or the prolonged bleeding times in these recipients. High vitamins C and K, avoidance of all unusual and unnecessary trauma, and maximum transfusion support and meticulous hemostasis by multiple ligation during emergency surgery are axiomatic.

Secondary Capillary Defects. Scurvy has long been known for its hemorrhagic manifestations, and there is no good reason for avitaminosis C to exist in modern society. Nevertheless, it occurs just often enough in the least expected places, in patients with food idiosyncrasies or careless restaurant dietary habits to need inclusion in an overall survey such as this.

200 to 500 mg. cevitamic acid daily by mouth or parenterally will promptly correct the acquired reversible capillary permeability defect in such patients. Abnormal capillary permeability may be relieved also at times by vitamin P—hesperidin or hesperidin methyl chalcone,—in 50 mg. capsules, the total daily dose being 100 to 200 mg. usually combined with ascorbic acid.

Mechanical Factors. In hypertension and in the vascular congestion which follows myocardial decompensation the integrity of the capillary bed is always threatened and is frequently violated. When purpura occurs under such circumstances, selective supportive measures are required. The one major contraindication to blood transfusions is myocardial decompensation. The hypertensive and cardiac factors must therefore be brought under control by appropriate measures at the earliest possible moment.

The physiologic integrity of the capillaries must be maintained by every known means under these adverse circumstances. Vascular endothelial continuity must be guaranteed by an excess of vitamin C (200 to 500 mg. daily), and vitamin P (100 to 200 mg. daily). Rutin (flavonal glycoside extracted from buckwheat) in 20 to 30 mg. doses every four hours is said

to assist in decreasing capillary fragility in these patients, though its precise pharmacologic action has not been satisfactorily demonstrated. Optimum prompt coagulation of any extravasated blood must be assured through parenteral vitamin K therapy (4 to 10 mg. daily). Local or generalized hypoxia affects the functional integrity of endothelial cells as it does all other tissues and organs in the body, and when this danger of cell damage is added to the mechanical factors in congestive failure—oxygen therapy is urgently indicated, as it is in all other purpuras when a low oxygen tension in the tissues results from an excessive loss, or inadequate oxygenation, of the circulating hemoglobin.

Anaphylactoid Purpura. Purpura on the basis of an antigenic hypersensitization mechanism may occur: (1) secondary to specific megakaryocytic damage with a resultant thrombocytopenic purpura of central bone marrow origin; or (2) as the result of a generalized vascular endothelial sensitization, so-called "anaphylactoid purpura." A careful history, skin and dietary elimination tests for specific allergies may elicit one or more specific antigens which may then lead to avoidance or a specific desensitizing therapeutic regimen. More often than not, however, the antigenic specificity remains anonymous despite exhaustive testing.

When testing for a purpura producing antigen, a warning should be sounded relative to the extremely high degree of specific sensitization, which may develop in a patient to such drugs, for example, as Sedormid (see figure 5). In two instances in our own experience where this drug was suspected and an extremely small oral dose was repeated to establish it as the cause of a previous purpuric episode, a near fatal, generalized thrombocytopenic purpura was re-precipitated, lasting five to seven days, with widespread megakaryocyte damage. Forced fluids, to hasten elimination of the offending antigen, and supportive blood transfusions to supply platelets, are the treatment of choice and must be continued over the period required for megakaryocyte regeneration.

Lacking specific identification of the offending antigen, an autogenous urinary proteose concentrate may be obtained from such patients, during periods of active anaphylactoid purpuric exacerbations and, when antigenic specificity is demonstrated, through intracutaneous skin testing, a therapeutic desensitizing regimen may be instituted, which will induce, in some patients, a most gratifying remission for an indefinite period, even for years.

The anti-histaminic drugs may at times be helpful; for example, Benadryl capsules, 50 mg., three to four times daily for adults, the elixir 10 mg. to the dram for children; Pyribenzamine, 50 mg. tablets, elixir 5 mg. per dram; Neo-antigan 50 mg. dosage two to four times daily.

Histamine in the form of the diphosphate may be employed as a nonspecific desensitizing antigen: initial dosage 0.1 mg. subcutaneously, to be gradually increased at two to seven day intervals to 1 mg., or 2 mg. in 250 c.c. NaCl may be given, intravenously very slowly. The maintenance dose is 1 mg. once weekly.

High vitamins C and K are routinely indicated in every patient with anaphylactoid purpura. Hemorrhages from bowel and kidneys may at times require blood transfusion replacements.

Embolic Petechiae in Sepsis. Bacterial emboli produce a very specific type of readily identifiable petechial hemorrhage in skin and mucous membranes, in conjunctivae and nail beds, as, for example, in endocarditis lenta with the *Streptococcus viridans.* The toxemia of meningococcemia produces superficial ecchymoses and petechiae uniquely characteristic in type and distribution of an infectious agent. Isolation and identification of the specific organism and the prompt selection and administration of the appropriate chemo- or antibiotic therapeutic agent is the rational and only specific treatment for this type of purpura.

One of twin brothers, aged two years (figure 11) was admitted to the University Hospital with a generalized purpuric syndrome at about the same time and under circumstances similar to those already described for the patient with hypersplenic

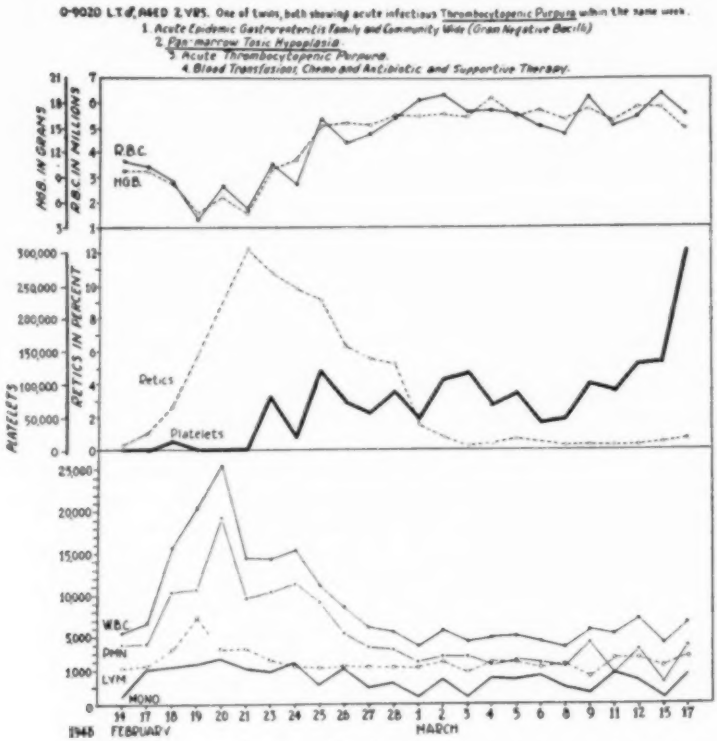


FIG. 11.

thrombocytopenia (figure 9). A non-hemorrhagic epidemic of enteritis, in community and home, had been communicated to the twins, each of whom promptly developed a marked bleeding diathesis with the infection. Again the circulating platelets were found to be extremely low or absent, but in this instance bone marrow studies revealed a central toxic picture affecting all cell types. The megakaryocytes were scarce and showed both nuclear and cytoplasmic degenerative vacuolization. Meticulous nursing care, supportive fresh whole blood transfusions and chemo- and antibiotic therapy resulted in the gradual regeneration of the essential marrow elements, followed by a return of platelets to the circulation with the permanent disappearance of all purpuric manifestations. Splenectomy under these circumstances would be fatal.

Endocrine Deficiency. Excessive uterine hemorrhage may occur as a part of any generalized purpuric syndrome in which platelet or plasma coagulation defects can be demonstrated, or it may present as a sometimes confusing, exsanguinating dysfunction, with minimal or no coagulation abnormalities, to be classified nevertheless as a "purpuric" manifestation. For immediate control, to arrest serious functional hyper- and polymenorrhea: (1) Ergotrate, grs. 1/320 every 4 to 12 hours, for not more than eight consecutive doses without 24 hr. rest period; (2) obstetrical pituitrin or pitocin, 1 ampoule, intramuscularly every 4 hrs., as long as necessary; (3) calcium gluconate or chloride, 10 c.c. 10 per cent solution intravenously. There is no incompatibility if the administration of all three of these agents is required in the same patient. For less urgent action effective within two to three days: testosterone 25 mg. per day; or antuitrin S, one or two ampoules daily; or stilbestrol, 5 to 10 mg. daily. A mild hypothyroid state is commonly associated with this syndrome and small doses of one-half to one gr. desiccated thyroid frequently are sufficient to readjust the responsible endocrine disequilibrium. Gynecologic consultation and examination are indicated when the hematologic coagulation mechanism has been eliminated as a precipitating or contributing factor in hypermenorrhea.

The informed physician and surgeon today may approach the patient with a hemorrhagic diathesis with a degree of assurance and confidence heretofore impossible, due to the increasing ease of quantitative evaluation and specificity of control of each individual factor in the complex physiologic mechanism of coagulation.

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STUDIES ON THE MECHANISM OF CARDIAC INJURY IN EXPERIMENTAL HYPOTHERMIA *

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THERE are numerous reports in the literature that subsequent to exposure to severe cold accompanied by a lowering of body temperature severe cardiac irregularities or sudden death may occur. These effects may occur even up to 24 hours after the exposure when the body temperature has long since returned to normal.[1-6] Such instances were encountered during the war with previous exposure to cold water (immersion) or with certain therapeutic uses of cold as an adjuvant in the treatment of malignancy. Numerous investigators have attempted to explain the hypothermic death but no single theory has found general acceptance.

Ariel, Bishop and Warren [7] report that in rabbits lowering of body temperature by immersion into cold water leads to a slowing of the heart rate with widening of the QRS complexes and marked prolongation of the S–T segments. Smith reports [4] similar observations in humans treated with crymotherapy and he states that death immediately after the therapy or within 24 hours is due to an anoxia caused by a decreased cardiac output. On autopsy of such patients who also had a marked reduction in respiratory rate neither the heart nor the cerebrum showed any remarkable changes. Clark [8] states that lowering of body temperature in the frog results in a reduction of heart rate, in a slowing of conduction, a decrease in force of contraction and a decrease in oxygen consumption. He states specifically that the rate is not a linear function of blood temperature in the rabbit or the frog. The most detailed data on the influence of lowered body temperature on the heart in humans are given by Kossmann [5] who noted the marked venous constriction which makes the taking of blood samples so difficult. He states that there is a linear relationship between body temperature and the length of the electrical systole as expressed by Bazett's formula. The T waves in his patients were markedly lowered with lowered body temperatures and the S–T segments became depressed. Auricular fibrillation was observed in four out of nine patients subjected to crymotherapy and Kossmann states that changes especially in the Q–T interval occurring in cooling may persist long beyond the lowering of body temperature. Tomaszewski [6] reports a case dying from exposure to cold in which the P–R interval and the intraventricular conduction time were

* Received for publication December 16, 1948.

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Carried out under a contract between the Research and Development Board of the Surgeon General, U. S. Army and the New York Medical College.

markedly prolonged and severe changes in the T waves had appeared; in spite of rewarming and an increase of pulse rate from 21 to 44 per minute the patient died. On autopsy no significant changes were discovered in the heart. Hook and Stormont [9] report progressive prolongations of P–R intervals and QRS complexes with cooling and bizarre changes in T wave patterns with deep inversions of T. They also attribute these changes to anoxemia due to slowing of respiration. Hamilton, Driebach and Hamilton [10] report a linear relationship between body temperature and heart rate and a general slowing of conduction with lowered temperatures in rats and kittens. They suggest that the cause for these changes is anoxemia induced by cold narcosis of the medullary centers. Crismon [11] describes that in experiments on rats the lowering of the body temperature is followed by a progressive slowing of the rate and prolongation of conduction, whereby the heart rate-temperature relation is linear. Blood pressure fell rapidly after an initial rise due to shivering and the author attributes death under such conditions to circulatory failure with subsequent regional asphyxia. Lutz and Werz [12] in contrast to all other observers draw the attention to the fact that with lowered body temperature the oxygen dissociation decreases and that this fact alone is theoretically able to explain death due to cold.

Our own experiments were stimulated by the observation that some animals, one limb of which was exposed to circulating cold water to produce trench foot, were unable to maintain their body temperature. They showed a gradual fall in temperature over a period of several days.[13] Electrocardiograms taken at regular intervals in such animals showed some outstanding changes. The rate became slower in a direct linear relation to their body temperature with the exception that in some of them there was an initial rise in pulse rate apparently due to shivering. Very soon, however, the linear relation was established with striking accuracy. The P–R intervals as well as the QRS complexes became progressively longer although the establishment of a direct mathematical relation is somewhat difficult due to the inherent errors in measuring such small intervals. In general, however, it may be said that in these prolonged exposures with slow reduction in body temperature the conduction slows proportionally to the reduction in body temperature (table 1, figure 1). The most significant changes, however,

TABLE I

Rabbit with One Leg Immersed in Running Water of 2°C. Loss of Body Temperature during 48 Hours and Changes in the Electrocardiographic Components

Body Temp., °C.	RR, sec.	Rate per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
38.3	0.30	200	0.06	0.03	0.14	0.26
35.5	0.224	268	0.06	0.03	0.12	0.25
32.0	0.35	172	0.07	0.03	0.19	0.32
26.0	0.50	120	0.09	0.04	0.28	0.40

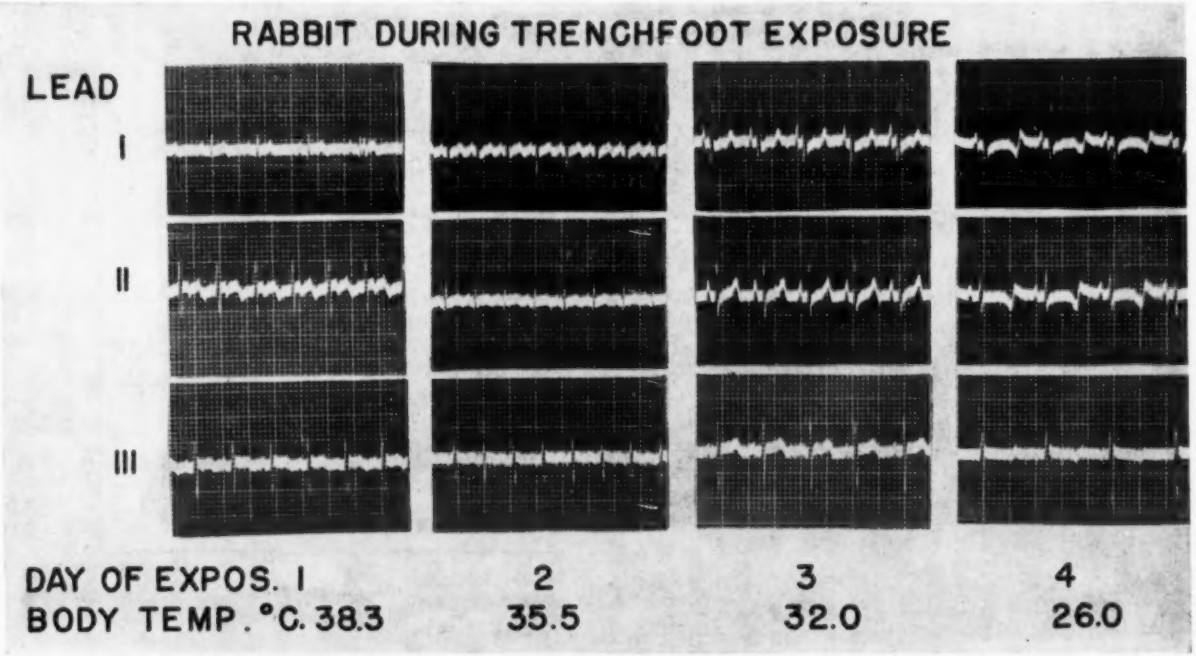

FIG. 1. Electrocardiograms of a rabbit during trenchfoot exposure with general loss of body temperature.

occur in the duration of electrical systole as determined by Bazett's formula $QT/\sqrt{RR}$. The systole becomes a progressively longer part of the cycle although the relation is not linear with body temperature as will be shown later. The T wave changes are most outspoken. From a lowering of T to a depression of the S–T segment to a sharp inversion of the T wave the changes move in a manner highly suggestive of progressive anoxia. At the same time the respiratory rate in such animals drops markedly although not in a linear relation to body temperature. In order to investigate these circulatory changes further, 28 clipped rabbits of four to six pounds body weight were exposed in a cold chamber to a temperature of $-20°$ C. frequently under pentothal sodium anesthesia to avoid electrocardiographic artefacts due to shivering. The survival time in such exposures is approximately two hours. In initial experiments it was demonstrated that this anesthesia in the dose given (1 to 1.5 c.c. nembutal per 5 pounds of body weight intraperitoneally) did not change the electrocardiogram during a similar period of observation when no cooling was used. The first group of animals was observed without artificial respiration and without anesthesia. They showed a constant relation between body temperature and respiratory rate which is shown in figure 2. The heart rate and the body temperature showed throughout the experiments a linear relationship as demonstrated in the example of one experiment in figure 3. This fact remained unaltered whether the animals were exposed with or without artificial respiration. The

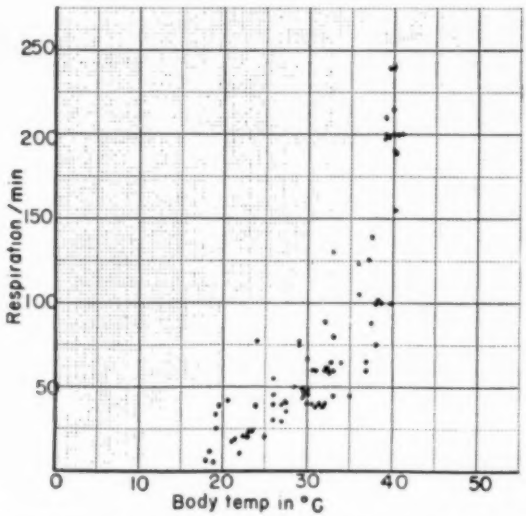

FIG. 2. Relation between respiratory rate and body temperature in 12 clipped rabbits exposed to an air temperature of $-20°$ C.

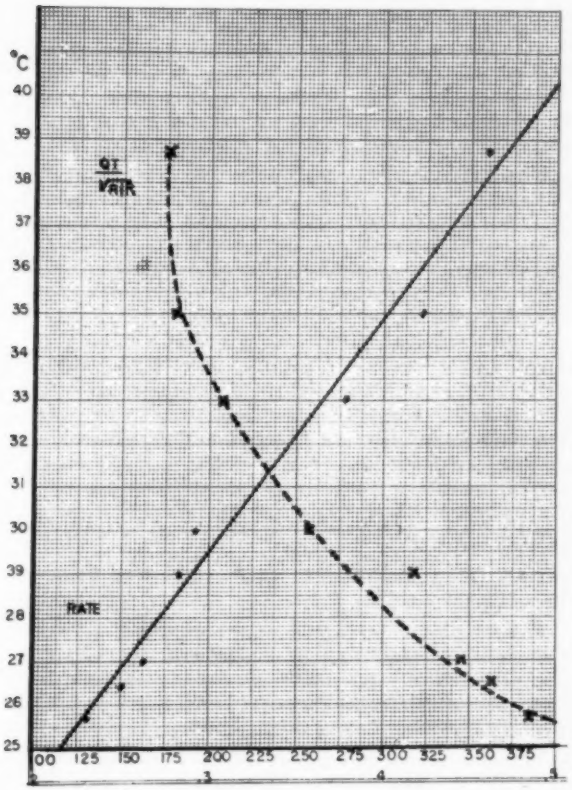

FIG. 3. Relation between body temperature, heart rate and electrical systole in a clipped rabbit exposed to an air temperature of − 20° C. Rewarming on electric heating pad.

slope of the curve permitted an exact prediction as to when heart standstill and death would occur and in those experiments which were carried to death under artificial respiration this prediction proved to be correct. The fact that artificial respiration at a constant rate did not influence the drop in heart rate proves that anoxemia does not have an influence on this relation. The P–R intervals and the QRS complexes became progressively longer in roughly a straight line relation to body temperature. The QT interval as evaluated by Bazett's formula showed changes which indicate a marked prolongation of systole during each cycle progressing with falling body temperature. The relation, although not linear, is a function of the temperature such that the systole is relatively more prolonged at lower temperatures (figure 3, table 2). These relations of prolongation of P–R

TABLE II

Clipped Rabbit under Pentothal Sodium Anesthesia Exposed to an Air Temperature of −20°C. Rewarming on an Electric Heating Pad. Changes in the Electrocardiographic Components

Time (min.)	Body Temp., °C.	RR, sec.	Rate, min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
0	38.7	0.167	360	0.07	0.02	0.11	0.28
100 (cooling)	26.5	0.45	134	0.09	0.03	0.31	0.46
8 (heating)	25.7	0.47	129	0.11	0.04	0.33	0.49
20 (heating)	27.0	0.37	163	0.08	0.03	0.27	0.45
32 (heating)	29.0	0.39	155	0.08	0.03	0.26	0.42
40 (heating)	30.0	0.31	193	0.08	0.03	0.20	0.36
70 (heating)	33.0	0.22	277	0.07	0.02	0.15	0.30
78 (heating)	35.0	0.19	322	0.07	0.02	0.12	0.28

intervals, QRS complexes and electrical systole were not altered by the introduction of artificial respiration (table 3). This demonstrated that slowing of the respiratory rate is not a factor. Blood calcium levels taken in seven animals before and during the cooling remained unchanged indicating that hypocalcemia does not play a rôle in the prolongation of the Q–T interval. In contrast to the mathematical constancy observed in the P–R, QRS, QT, and rate changes, the T wave alterations varied in individual animals. The lead most affected was not always the same nor was the degree of abnormality constant. Lowering of the T waves, S–T segment depression, flattening and deep inversion were all observed. Again artificial respiration even with pure oxygen did not prevent or alter this indicating that these changes which give the distinct impression of being *anoxic* in nature are not due to an *anoxemia*. There was not a single animal that failed to show these T wave alterations to a considerable extent.

The anoxia may be due to a lowered oxygen dissociation. Barcroft and King were able to demonstrate that with lowering of body temperature the oxyhemoglobin dissociation decreases rapidly. The available oxygen at a tissue oxygen tension of 40 mm. Hg is, e.g., 27 per cent at 36° C. while

TABLE III

Clipped Rabbit under Pentothal Sodium Anesthesia and Artificial Respiration Exposed to an Air Temperature of −20°C. Acid Sodium Phosphate Injected after Severe Lowering of Body Temperature

Body Temp., °C.	RR, sec.	Rate, per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
35	0.25	240	0.06	0.02	0.15	0.30
27	0.53	113	0.09	0.03	0.32	0.44
23	0.90	67	0.11	0.04	0.52	0.55
22.5 (immediately after injection of 5 c.c. of 1N NaH_2PO_4)	1.1	55	0.15	0.06	0.56	0.53
22.2 (2.5 minutes after injection)	0.88	68	0.13	0.06	0.50	0.53

at 20° C. it is only 3 per cent (figure 4). This means that although the hemoglobin is fully saturated with oxygen it is unable to release it to the tissue. We may then be dealing with an anoxia without anoxemia. It is interesting to note that poikilothermic animals have a much higher oxygen dissociation at low temperatures than homoiothermic animals thus enabling them to supply oxygen to their tissues even at low body temperatures.

The possibility occurred to us that Cytochrome C may be able to help the transfer of the oxygen from the hemoglobin to the tissue. Six animals were therefore given 2 to 4 c.c. of Cytochrome C (Wyeth) after they were cooled to a body temperature of approximately 25° C. The electrocardiographic changes were not in the least improved by this treatment.

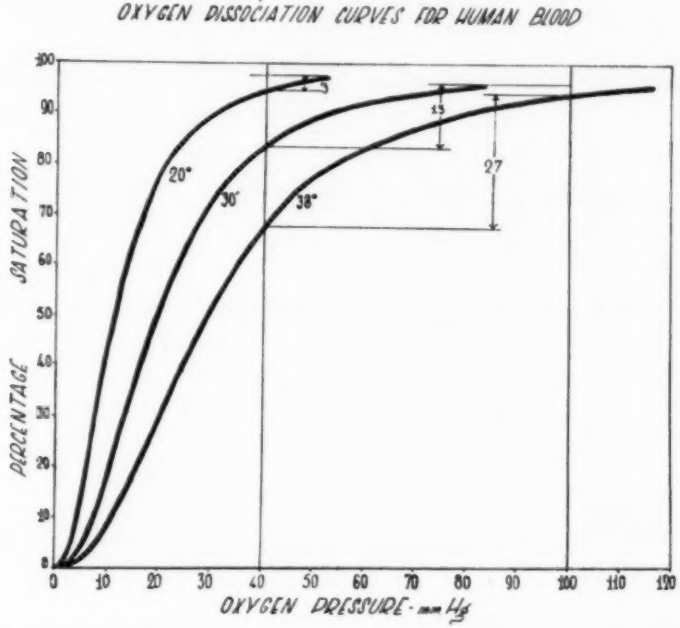

FIG. 4. Oxyhemoglobin dissociation curves for human blood at various temperatures.

We attempted to compensate for the lowered oxygen dissociation by increasing the amount of oxygen physically dissolved in the plasma independent of the hemoglobin. We calculated that this would require a 25 fold increase in the partial pressure of oxygen in the inspired air. This was accomplished by placing a severely cooled rabbit in a compression chamber containing 100 per cent oxygen at a pressure of 75 pounds per square inch.

Within seven minutes the abnormal electrocardiogram had improved markedly and on subsequent decompression to a normal atmosphere the anoxic pattern reappeared (figures 5 and 6).

Since acidification of the blood is known to produce an increased oxygen dissociation, i.e., to act just in the opposite direction of reduction of temperature, an attempt was made to acidify the blood of animals when they

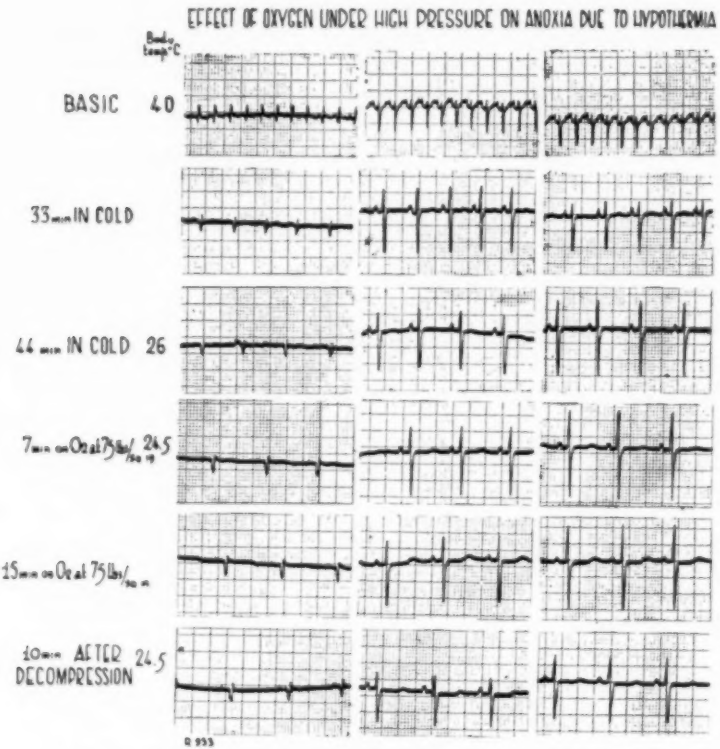

FIG. 5. Electrocardiograms (limb leads) of a rabbit before and after hypothermia and before and after exposure to an atmosphere of 100 per cent oxygen under a pressure of 75 lbs. per sq. inch.

showed the severe T wave changes at low body temperatures. Five to 10 c.c. of acid sodium phosphate (NaH_2PO_4) in .5 or 1 N concentration were injected intravenously in 11 rabbits. Seven of these animals were examined with artificial respiration. In all of them the injection caused an immediate short lasting but very clear-cut return of the T waves to or towards normal (figures 7 and 8). The injection also caused a short-lived hyperpnea in

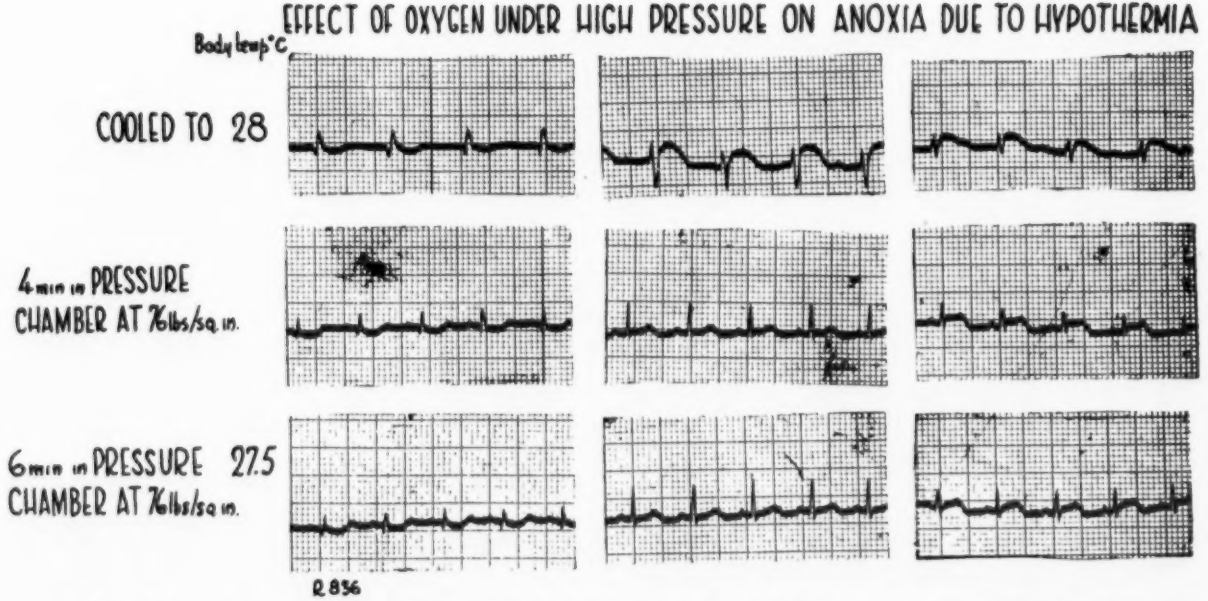

FIG. 6. Electrocardiograms (limb leads) of a rabbit after hypothermia and before and after exposure to an atmosphere of 100 per cent oxygen under a pressure of 75 lbs. per sq. inch.

those animals which were not under artificial respiration, so that the objection could be raised that the improvement was due to respiratory relief of anoxemia. Such an objection is not valid, however, in the seven animals which were under artificial respiration. Here the influence of the acidification by NaH_2PO_4 alone must be considered the cause of the reversal of the

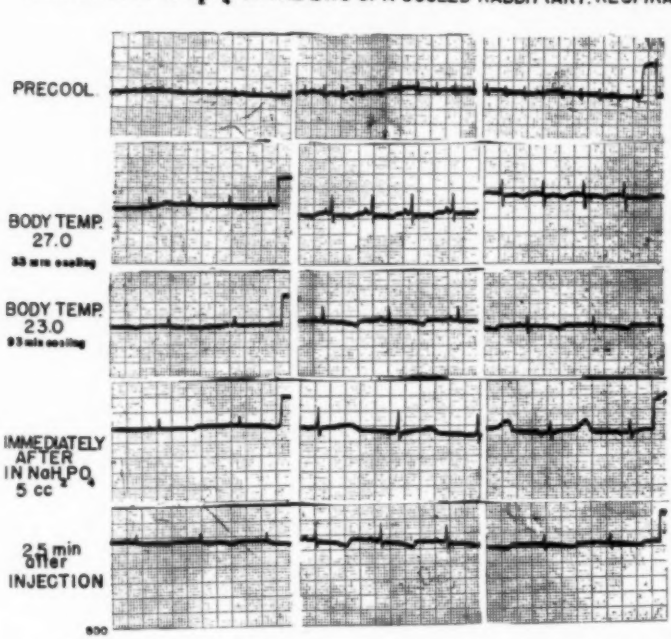

FIG. 7. Electrocardiograms of a clipped, anesthetized rabbit under artificial respiration exposed to an air temperature of $-20°$ C. After a severe hypothermia NaH_2PO_4 is injected.

T waves towards normal. At the same time the injection produces a further slowing of the rate and a further prolongation of the P–R interval. The relative length of the electrical systole, however, is shortened by the acidification (table 3 and 4). Similar results can be obtained by injecting 1/10 N hydrochloric acid or by administering 20 per cent gluconic acid. That the injection of NaH_2PO_4 alone in a normal uncooled anesthetized animal under artificial respiration does not produce any T wave or other electrocardiographic changes was shown in two animals (table 5).

Measurements of the pH of the arterial blood of such animals before and after the intravenous injection of acids revealed a lowering of the pH by 0.2 to 0.9 in individual experiments.

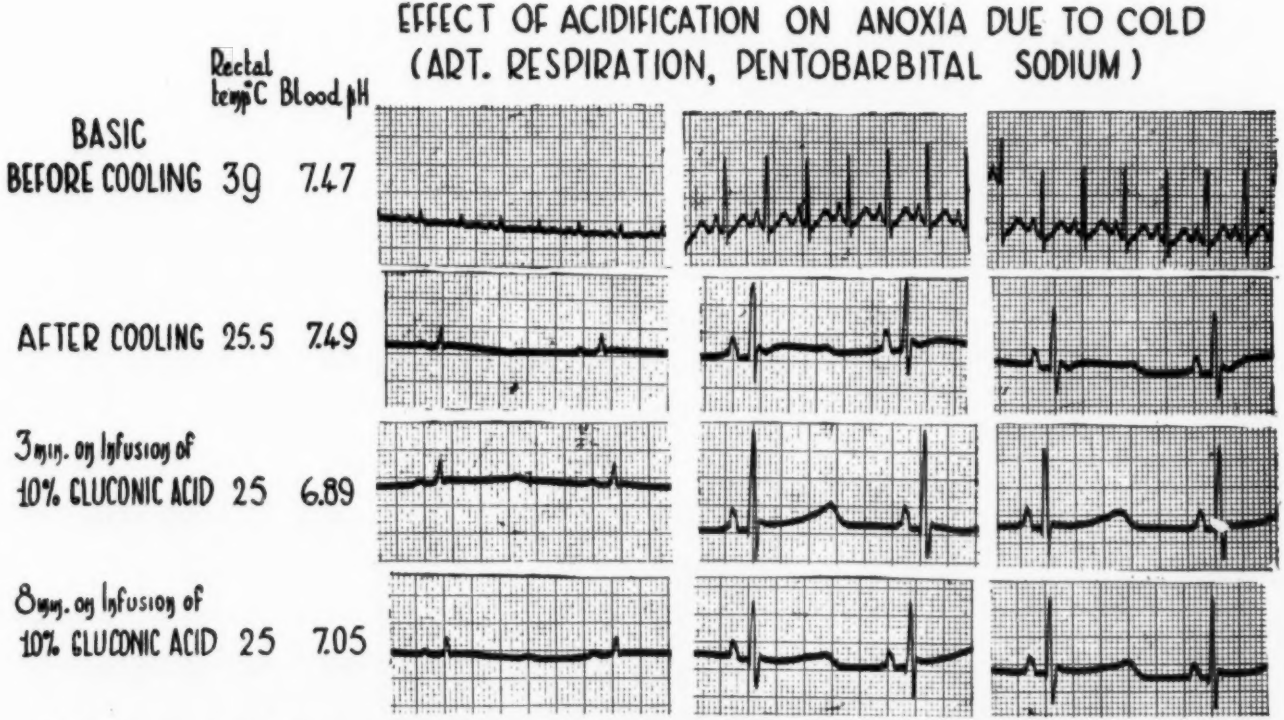

FIG. 8. Electrocardiograms of a clipped, anesthetized rabbit under artificial respiration exposed to an air temperature of −20° C. After a severe hypothermia NaH_2PO_4 is injected.

TABLE IV

Clipped Rabbit under Pentothal Sodium Anesthesia and Artificial Respiration Exposed to an Air Temperature of −20°C. Acid Sodium Phosphate Injected after Severe Lowering of Body Temperature

Body Temp., °C.	RR, sec.	Rate, per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
36	0.31	193	0.08	0.02	0.20	0.36
24.6	0.69	81	0.10	0.04	0.46	0.55
24 (immediately after injection of 5 c.c. of 1N NaH_2PO_4)	0.85	71	0.12	0.04	0.48	0.52
24 (4 minutes after injection)	0.87	69	0.12	0.04	0.48	0.515

TABLE V

Influence of an Injection of Acid Sodium Phosphate on an Anesthetized Clipped, not Cooled Rabbit

Time	RR, sec.	Rate, per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
Before injection	0.24	250	0.07	0.02	0.15	0.31
30 seconds after injection of 5 c.c. of 1N NaH_2PO_4	0.27	222	0.07	0.03	0.15	0.29
90 seconds after injection	0.25	240	0.07	0.03	0.15	0.30
2.5 minutes after injection	0.25	240	0.07	0.02	0.15	0.30
6 minutes after injection	0.27	222	0.07	0.02	0.16	0.31

Experiments in dogs, which will be reported separately, revealed identical EKG changes and pH deviations.

CONCLUSIONS

From these experiments it is evident that lowering of body temperature in rabbits is accompanied by a proportional fall in pulse rate which permits an exact prediction of the temperature at which heart-standstill will occur. This relation in rate is not due to anoxemia and not improved by availability of oxygen by means of acidification of the blood. Thus it is dependent only on the direct effect of the cold on the pacemaker or its governors. The relationship to temperature also holds true for the changes occurring in the P–R interval and the QRS complex. They too seem to be directly and exclusively dependent on the effect of the temperature on the specific conduction system. Anoxemia and relief of anoxia do not influence these factors. The length of systole increases markedly but not in linear relation with cold. It is to a larger extent produced by a direct influence of the lowered temperature on the muscle. To a certain extent, however, anoxia favors this extension of systole in the cycle. With relief of anoxia the length of systole is shortened, i.e., the sluggishness of the muscular contraction is improved. The T wave changes seen in cold are entirely the result of

anoxia for they can be completely reversed by making oxygen available through acidification of the blood with subsequent improvement of the oxygen dissociation or by increasing the amount of oxygen physically dissolved in the plasma. It is therefore possible that the reported deaths subsequent to severe exposure to cold are due to longstanding anoxic damage of the heart muscle too early to be detected by present morphologic methods.

In patients recovering from hypothermia it may therefore be advisable to treat them for a short period of time as if they had myocardial infarctions.

Summary

1. The literature on the influence of hypothermia on cardiac rate, conduction and the myocardium is reviewed.

2. Rabbits suffering from slow or rapid lowering of body temperature show a reduction in heart rate directly proportional to the fall of body temperature.

3. The P–R interval and the QRS complex are also roughly proportional in their prolongation to the fall in body temperature.

4. The relative prolongation of electrical systole is not a linear function of body temperature. It becomes relatively more prolonged at lower body temperatures.

5. The very marked changes in the S–T segment and the T wave under such conditions show individual differences in extent and localization.

6. The changes in rate and conduction are exclusively the result of the direct effect of cold. The prolongation of electrical systole is partly the result of cold directly on the muscle fibers and partly the result of anoxia due to lowered oxygen dissociation. The T wave changes are exclusively the result of anoxia.

7. The anoxic nature of the S–T segment and T wave changes as well as part of the prolongation of electrical systole is proved by the fact that increasing the oxygen dissociation of the blood by acidification reverses them to normal. Increasing the amount of oxygen physically dissolved in the plasma also reverses these changes.

8. Acidification of the blood does not change the electrocardiogram of uncooled rabbits.

9. Anoxemia plays no rôle in the production of any of the changes seen in the heart with exposure to cold. We are dealing with anoxia without anoxemia.

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CORONARY OCCLUSION AND MYOCARDIAL INFARCTION ASSOCIATED WITH CHRONIC RHEUMATIC HEART DISEASE*

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ALTHOUGH isolated cases have been reported (Kerr et al., 1925; Breitenecker, 1931), coronary artery obstruction has long been regarded as an uncommon complication in rheumatic heart disease. White and Jones (1928) found only one patient who had suffered a coronary thrombosis in 956 cases of rheumatic endocarditis. Among 99 patients dying with pure aortic stenosis Contratto and Levine (1937) reported four instances of coronary occlusion, and in 314 consecutive cases of simple mitral stenosis (Levine and Kauvar, 1941) coronary occlusion was diagnosed in only 10 instances (confirmed at autopsy in five). Rheumatic heart disease is found in less percentage still among patients with coronary heart disease. Only recently Cassidy (1946) reported that in 2000 cases of coronary heart disease he has not seen a single instance of concomitant chronic rheumatic endocarditis.

There seems no a priori reason why middle-aged and elderly patients with rheumatic heart disease should not develop coronary artery atherosclerosis as frequently as others without rheumatic stigmata. Indeed, since right and left ventricular hypertrophy commonly follow rheumatic valvular lesions, it might even be supposed that the latter condition would predispose to coronary insufficiency. Moreover, if, as Zeek (1932) and Karsner (1934) have claimed, acute rheumatic fever is attended by widespread lesions of the coronary arteries and predisposes to precocious coronary sclerosis, it might be assumed that patients with rheumatic heart disease would be unduly liable to coronary thrombosis and that this liability would become apparent at an earlier age than is usual in uncomplicated degenerative coronary disease. The reported figures suggest that coronary occlusion is infrequent in rheumatic heart disease; it is noteworthy, however, that with the exception of Levine's and Kauvar's five autopsied cases the figures are based on clinical diagnoses alone.

It is our belief that, in the absence of signs of gross valvular lesions, the presence of rheumatic heart disease may be overlooked in elderly patients and hence the real frequency of the association of this condition with coronary heart disease, if based on clinical records alone, may be underestimated. We have, therefore, made a study of necropsy material and compared the results with our more recent clinical records in order to check any discrepancy in our clinical findings. We also hoped to obtain a clearer picture of the relationship, if any, between rheumatic and coronary heart disease.

* Received for publication June 3, 1948.

Material. I. Necropsy Series

In 6,000 consecutive autopsies at the Massachusetts General Hospital there were 436 patients dying with rheumatic heart disease and 513 patients dying with coronary heart disease.* Thirty-two patients were found to have both rheumatic and coronary heart disease. Thus, in this series, about 7 per cent of patients with rheumatic heart disease also suffered from coronary heart disease, and about 6 per cent of patients with the latter condition had accompanying rheumatic endocarditis.

Clinical Findings. In this group of 32 patients with rheumatic and coronary heart disease, 15 were male and 17 female, and their ages ranged from 42 to 82 years, with the greatest incidence in the sixth and seventh decades. Nine patients had a history of acute rheumatic fever and/or rheumatic heart disease, and angina pectoris. Seven had a history of rheumatism alone, eight of angina pectoris alone, and eight patients had nothing in their histories to suggest either condition. Five of the 32 patients had a history of old myocardial infarction.

Relevant physical findings, aside from the signs of valvular disease, were hypertension in 13 patients and arrhythmias in 16.

Auricular fibrillation was present in 14 patients. Nine of these were under observation for months or years. Auricular fibrillation started in one patient after a posterior myocardial infarct nine months before death, and two patients, known to have had rheumatic heart disease, had auricular fibrillation for seven months and four years respectively before death. In the six remaining cases the onset of auricular fibrillation was terminal. Five patients were seen only during the final illness when auricular fibrillation was present throughout the period of observation.

Complete auriculoventricular block was found in one patient. This was a man of 57 who died as a result of myocardial infarction. The heart block was known to have been present for at least two years.

Paroxysmal tachycardia was present in one patient who was under observation for only four weeks before death.

Electrocardiograms (standard leads and in a few instances CF_4) of 25 patients were relevant in relation to the coronary accident so far as could be judged from the autopsy specimens. In 21 cases of myocardial infarction 11 records showed changes characteristic of this condition and six were suggestive. In the four cases with coronary occlusion without infarction, one electrocardiogram showed evidence of myocardial changes, two showed auricular fibrillation and digitalis effects, and the fourth, from a patient with known mitral and aortic valve disease, showed left bundle branch block.

Pathological Findings. Autopsy examination revealed rheumatic lesions of both mitral and aortic valves in 23 of the 32 hearts; the aortic valves were

* For the purpose of this study the designation "coronary heart disease" was limited to cases in which there was either myocardial infarction or coronary occlusion without infarction.

affected alone in five hearts and the mitral valves alone in four. Mitral stenosis was judged to be present in 13 cases and aortic stenosis in eight. Using White's criteria (1944) for the measurements of the valve circumferences we would consider only seven patients to have had clinically important mitral stenosis, that is, a circumference of the mitral orifice of less than 7.5 cm., and in no case was the aortic ring less than 5 cm. in circumference. Myocardial infarction was found in 25 hearts. In 12 the infarcts were recent, in eight they were of long standing, and in five there were both old and recent infarctions. In all but three cases the left ventricle bore the brunt of the infarctive process and anterior wall infarctions (19) were found with slightly greater frequency than posterior (15). Widespread atherosclerotic disease of the coronary arteries was found in all but one instance. In eight hearts no actual occlusion of the coronary artery could be demonstrated, but in nine two or more large vessels were thrombosed.

Correlation of Clinical with Pathological Findings. A correct antemortem diagnosis of combined rheumatic and coronary heart disease was made in only seven of the 32 patients. Coronary heart disease alone was diagnosed in 20 cases, rheumatic heart disease alone in four, and in one patient who died of a cerebral accident after a vaginal hysterectomy neither condition had been suspected during life. In only five cases was there failure to recognize the coronary heart disease, though in 10 the presence of recent myocardial infarction was unsuspected. Rheumatic heart disease was unrecognized in 21 of the 32 patients, and mitral stenosis was missed in three of the seven patients where definite postmortem evidence of considerable stenosis was present.

TABLE I

Showing (I) Age and Sex Distribution of Patients Dying with Uncomplicated Coronary Heart Disease, Uncomplicated Rheumatic Heart Disease, and Combined Rheumatic and Coronary Heart Disease in 6,000 Consecutive Autopsies at the M. G. H. and (II) Age and Sex Distribution in 57 Patients with Combined Rheumatic and Coronary Heart Disease in 10,000 Consecutive Cases Seen in the Private Practice of P. D. W.

Age	I Necropsy Series									II Clinical Series
	Uncomplicated Coronary Heart Disease			Uncomplicated Rheumatic Heart Disease			Rheumatic and Coronary Heart Disease			Rheumatic and Coronary Heart Disease
	All	M	F	All	M	F	All	M	F	
Under 40	11	10	1	122	61	61	0	0	0	0
40–49	34	30	4	69	36	33	2	2	0	2
50–59	115	90	25	88	49	39	12	6	6	30
60–69	179	128	51	75	45	30	13	5	8	16
70–79	119	79	40	41	24	17	2	0	2	9
80–89	23	13	10	9	5	4	3	2	1	0
Total 40 years and over	470	340	130	282	159	123	32	15	17	(M 40; F 17) 57

It should be noted that these patients were admitted on medical, surgical, and gynecological services, and although the cardiological group were able to examine some of them others were under the care of physicians or surgeons more directly interested in other fields.

Sex and Age Incidence of Coronary and Rheumatic Heart Disease in the Autopsy Series. The table shows the sex and age distribution of all patients dying with uncomplicated coronary heart disease, uncomplicated rheumatic heart disease, and coronary and rheumatic heart disease combined among the 6,000 autopsies.

It can be seen that there were 282 persons of 40 years and upwards dying of rheumatic heart disease, 123 of whom were females. There were 470 persons in the same age group dying with uncomplicated coronary heart disease, and only 130 of these were women. Among the patients with combined lesions there was no instance of coronary occlusion or myocardial infarction under the age of 40, and the highest incidence of this combination occurred in the sixth and seventh decades, roughly corresponding to the incidence for the cases of uncomplicated coronary heart disease.

II. Clinical Series

We have examined the records of 10,000 cardiovascular cases seen in the consulting practice of one of us (P. D. W.) to discover how frequently the diagnosis of combined rheumatic and coronary heart disease has been made. Among the 10,000 cases there were 2,840 instances of coronary heart disease, 1,346 of rheumatic heart disease, and only 57 patients (40 men and 17 women) where both conditions could be diagnosed with certainty. In this series, therefore, only 2.0 per cent of patients with coronary heart disease had clinically recognizable rheumatic heart disease, in contrast to the 6 per cent found in our autopsy series. On the other hand, 4.2 per cent of the patients with rheumatic heart disease had a diagnosis of accompanying coronary heart disease, a proportion corresponding more closely with our autopsy findings.

The difficulty of making the dual diagnosis may be illustrated by the following patient who has been under observation for the past 10 years.

Mrs. H. G., aged 68, first consulted us in 1937 for breathlessness on exertion and general fatigue. She gave a history of rheumatic fever at the age of 12 and again at 49 and of high blood pressure for a few years. Cardiological examination in 1937 showed a slightly enlarged heart with regular rhythm, normal heart sounds, and a slight aortic systolic murmur; blood pressure 170 mm. Hg systolic and 100 mm. diastolic. In February 1942 she had an acute myocardial infarction confirmed by characteristic electrocardiographic changes. She made a fairly satisfactory recovery, but for the next 18 months she complained of fatigue and suffered recurrent bouts of moderate left ventricular failure. In September 1943 she was in fair health again but on examination Grade III systolic and Grade I diastolic murmurs were audible for the first time in the aortic area. At subsequent examinations only a moderate aortic systolic murmur and no diastolic murmur was heard. She continued to have mild left ventricular failure until she was admitted to the hospital in June 1945 for surgical treatment of carcinoma of the rectum. At this time the aortic systolic and diastolic murmurs were again heard, and in addition there was a Grade I mitral

diastolic murmur with definite presystolic accentuation, and the diagnosis of rheumatic heart disease with slight aortic stenosis and regurgitation and slight mitral stenosis was made. Since that time the same murmurs have invariably been present, though often very careful auscultation has been necessary to detect them.

We now think it possible that a recurrent smoldering rheumatic carditis may have been partially responsible for the periods of ill health and left ventricular failure to which this patient was subject, but the hypertension and the myocardial infarction had been thought to be sufficient explanation for her condition until unequivocal evidence of valvular disease appeared. Had this complication been in mind, it is possible that a more diligent search might have revealed characteristic murmurs at an earlier date.

Discussion

The small number of cases with completely accurate antemortem diagnosis in our autopsy series demands comment. That rheumatic heart disease was unrecognized in as many as 21 of 32 cases suggests a low index of clinical suspicion. It is true that only in seven instances was there any considerable stenosis of the mitral valve, but three of these were unrecognized during life. It is also true that several patients were moribund when first examined and any signs of valvular disease which may have been present were obscured by tachycardia, gallop rhythm, or pulmonary edema consequent upon acute myocardial infarction, but in these, so far as we know, the diagnosis of rheumatic heart disease had not been made prior to their coronary illness. Moreover, it may be difficult to diagnose rheumatic heart disease with certainty in elderly patients. A history of rheumatic fever in youth is frequently lacking; it was obtained in only five of the undiagnosed cases. The presence of auricular fibrillation is of little assistance, for in this age group this arrhythmia may be due to a number of causes other than rheumatic heart disease with mitral stenosis. In our series it was found in only three of the patients with unsuspected rheumatic heart disease where adequate observation was possible during life, and in these either coronary or hypertensive heart disease was thought to be sufficient explanation. Nevertheless, there is a certain unawareness of the possibility of combined rheumatic and coronary heart disease. In several instances the significance of basal and apical systolic murmurs was underestimated, and in three patients although aortic valve disease was recognized during life it was attributed to atherosclerotic changes rather than to rheumatic heart disease.

Although the numbers in our autopsy and clinical series are small, it is clear that we are still overlooking chronic rheumatic endocarditis among patients with coronary heart disease, for in the clinical series only 2.0 per cent of the patients with the latter condition had recognized rheumatic heart disease in contrast to the 6 per cent in the autopsy series. It might be questioned whether or not unrecognized rheumatic heart disease has any significance in patients under observation for coronary insufficiency. Certainly unrecognized recent myocardial infarction has more serious conse-

quences than unsuspected rheumatic heart disease, but smoldering rheumatic infection, even in elderly patients, may account for ill health and serious sequelae. This is illustrated by a patient with hypertensive and coronary heart disease recently seen by one of us (P. D. W.) where the sudden onset of auricular flutter precipitated acute pulmonary edema and the underlying rheumatic heart disease was only discovered after a careful search revealed the murmur of mitral stenosis. We can offer no easy way by which the diagnosis of rheumatic heart disease can be made in 100 per cent of cases. Electrocardiographic and roentgenological findings are, as a rule, not helpful; the rhythm is usually normal, right axis deviation is uncommon, and the left auricle is often not appreciably enlarged. We can only urge a more diligent search for the characteristic murmurs which are the hallmark of the condition.

An interesting feature of this investigation is the high proportion of female patients in the autopsy series with both rheumatic and coronary heart disease. That it is not due to a preponderance of women dying with rheumatic heart disease in these particular age groups, or to an unusual sex distribution in our series of patients dying with coronary heart disease, is shown in the table. Of the 282 persons 40 years of age and upwards dying with rheumatic heart disease, less than one half were female. Moreover, of the 470 persons in the same age group dying with uncomplicated coronary heart disease, less than one third were women. This sex distribution corresponds with the figures usually reported in large series of patients dying with these diseases. We are unable to offer any satisfactory explanation for the fact that over 50 per cent of the patients with both coronary and rheumatic heart disease in the autopsy series were women; the smallness of this group, only 32 in all, may be the answer. In our clinical series men outnumbered the women more than two to one. The discrepancy between the two groups might perhaps be explained by our failure to detect the presence of rheumatic heart disease in a number of women with coronary artery degeneration.

The frequency with which aortic valve disease was found at autopsy is noteworthy. Fourteen of the 15 men (93 per cent) and 14 of the 17 women (82 per cent) had lesions of the aortic valves. In 282 persons in the same age group dying with uncomplicated rheumatic heart disease, only 75 per cent of the men and 60 per cent of the women had aortic valvulitis. It is impossible to draw conclusions from such a small group of cases, but these facts suggest the possibility that patients over the age of 40 with rheumatic heart disease are more likely to develop serious coronary artery degeneration if the rheumatic lesion implicates the aortic valves.

It is clear from the table that this study provides no evidence in support of Karsner's view that rheumatic heart disease predisposes to premature coronary artery degeneration. In neither the autopsy nor the clinical series was there a single case of combined rheumatic and coronary heart disease under 40 years of age. We can only conclude that the presence of rheumatic heart disease has no direct influence on the incidence of degenerative disease of the coronary arteries.

Summary

1. In 6,000 consecutive autopsies there were 436 cases of rheumatic heart disease and 513 cases of coronary heart disease, 32 of which had both conditions (7 per cent of the rheumatics and 6 per cent of the coronary cases). Fifteen were male and 17 female.

2. In 10,000 consecutive clinical cases 1,346 were diagnosed as having rheumatic heart disease and 2,840 coronary heart disease, 57 of which had both conditions (4.2 per cent of the rheumatics and 2.0 per cent of the coronary cases). Forty were men, and 17 were women.

3. Aortic valve disease was found in 28 of the 32 fatal cases of combined coronary and rheumatic heart disease (87 per cent). It was present in only 69 per cent of the fatal cases of uncomplicated rheumatic heart disease. Mitral valve disease was found in 27 of the 32 (84 per cent).

4. A completely correct antemortem diagnosis was made in only seven of the 32 cases, although either rheumatic or coronary heart disease was diagnosed in 31 of the cases. The rheumatic heart disease was overlooked in 21 of the 32 patients.

5. Incomplete diagnosis was to some extent inevitable because of the moribund state of some of the patients when examined. To some extent it was probably also due to a common clinical unawareness that coronary and rheumatic heart disease may be associated.

6. The relatively low incidence of rheumatic heart disease among the coronary cases in the clinical series suggests that the former condition is still being overlooked in these patients.

7. Complete diagnosis is an important preliminary to satisfactory management. The value of careful auscultation in establishing the diagnosis of concomitant rheumatic heart disease is emphasized.

8. We have found no evidence to suggest that rheumatic heart disease has any influence on the development of coronary artery degeneration.

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THE SURGICAL REHABILITATION OF THE CORONARY CRIPPLE*

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REHABILITATION is being emphasized more and more in the treatment of disabled patients. The National Council on Rehabilitation has proposed the following definition of rehabilitation: "the restoration of the handicapped to the fullest physical, mental, social, vocational and economic usefulness of which they are capable." [1]

In general there are six groups [2] of the handicapped who need rehabilitation. They are: (1) the blind, (2) the deaf, (3) the neuropsychotic, (4) the tuberculous, (5) the orthopedic and, (6) the cardiacs. It is the purpose of this article to present our experience in the surgical rehabilitation of those cardiac patients who are crippled by the anginal pain of coronary artery disease.

The need for rehabilitation of these coronary cripples becomes apparent when we study their position in vital statistics. The latest figures which are available are for 1945.[3] In that year there was a total death rate for the United States of 1,401,719. The number one killer in this death rate is heart disease, which accounts for 424,328 or about 30 per cent of all deaths. In this group of heart disease deaths, coronary artery disease and angina account for 131,437, which is approximately 30 per cent of all heart deaths and 10 per cent of the total deaths in this year. It is estimated by the Metropolitan Life Insurance Company that in the United States in 1945 there were about four million known cases of organic heart disease. Between one-fifth and one-third or roughly from 800,000 to 1,400,000 of these have coronary artery disease. Not all of those coronary deaths were in patients who were incapacitated or crippled before death, for about 20 per cent of them die with the first attack. However, it seems fairly safe to assume that the vast majority of these patients were partially or completely incapacitated before death. It therefore becomes evident that there is a real need for rehabilitation of the "coronary cripple."

Rehabilitation for what? is the question that is frequently asked by the physician as well as the patient. We do not expect the coronary patient, crippled with angina, to become restored to a physical state beyond his former capacity. We do not expect a restoration which would allow competitive or very strenuous physical activities. We do not expect all coronary patients to be restored equally. We do have, however, a definite criterion of what does constitute rehabilitation for these patients and it consists of

* Received for publication August 19, 1948.

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the following: (1) a relief of anginal pain which may be partial or complete, (2) an increase in the exercise tolerance so that walking and ordinary travelling is possible, (3) the ability to care for the daily needs, (4) the return to some gainful occupation.

In the study and surgical rehabilitation of these patients, we have not attempted to classify angina according to its etiology. We believe that it is a result of coronary artery insufficiency which in turn produces a myocardial ischemia. The rationale of surgery in this situation is an attempt to overcome the myocardial ischemia by the production of a collateral circulation as well as the production of a myocardial hyperemia.

There have been many surgical attempts to produce a collateral circulation to the myocardium. The term "collateral" is used here in a broad sense, meaning the establishment of a new circulation in part, or a new or more efficient use of the old circulation. The theoretical weakness of these procedures is that they do not eliminate or check the continuing coronary artery disease although, in a mechanical way, they do correct the effects of the disease. Because the disease process is not eliminated, the surgical procedures cannot be considered as curative measures.

The collateral circulation can be produced in a number of ways, using a variety of technics and would appear to be the logical method in the treatment of coronary artery disease. The attachment of some vascular tissue to the heart is one of the essential features of almost all of the surgical procedures. Until recently the likelihood of producing a myocardial hyperemia as a definite part of the treatment has been overlooked.

Many tissues have been used to provide a new or collateral blood supply. Among them are skeletal muscles, omentum, intrathoracic tissue, lung or mediastinal fat, and the pericardium. Grafting tissue on the myocardium produces a collateral circulation in two ways: (1) Intra-cardiac, by the formation of new collaterals or by stimulating an increase in the size and function of these collateral channels which are already present in the heart; (2) Extra-cardiac, by the formation of new channels from the grafted tissues to the myocardium. Thus, by this method, the insufficient coronary flow is partially compensated by increasing the amount of blood supplied to the myocardium.

In our various experimental attempts to produce a collateral circulation we found, in the animals that survived the operations, two factors which were present in all the different methods. These were: (1) The surgical trauma and inflammation produced by the operation itself, which resulted in myocardial hyperemia; (2) The production of adhesions between the pericardium and myocardium. This led us to use the pericardium as the tissue from which to establish a collateral circulation.

Under normal circumstances, the pericardium is thin and appears to be almost avascular. However, the blood supply is abundant. It receives branches from the aorta, from the internal mammary, from the esophageal, from the phrenic, from the bronchial, from the mediastinal, and from the

coronary arteries themselves. These branches are ordinarily very small; nevertheless they constitute a rich source for collateral communication with the coronary arteries. Increase in the size and function of these vessels is similar to that seen in the vasa vasorum when the accompanying artery is sclerotic or stenosed.

Experimental Evidence

Adhesive pericarditis may not be readily or easily produced in every instance by mechanical trauma or a host of chemical irritants. In a series of animal experiments which have been previously reported,[4] we attempted to find a satisfactory method for producing adhesive pericarditis and thereby grafting the pericardium on to the myocardium and finally decided upon the intrapericardial use of U.S.P. talc powder (hydrous magnesium silicate) for a number of reasons. The following results occurred constantly and therefore we considered the use of (U.S.P.) talc powder to be dependable. When introduced into the pericardial sac, talc powder produces a foreign body reaction, characterized by marked hyperemia and a fibrinous pericarditis, with little or no fluid formation. As early as 18 hours after the introduction of the powder, the pericardium becomes adherent to the epicardium at the site of the powder. After one week the two surfaces are firmly adherent, and after four weeks the pericardium and epicardium are fused as one layer of tissue. The constancy with which the powder produces an inflammatory reaction with little or no fluid formation is remarkable. This is very desirable since the presence of fluid within the pericardial sac would prevent the formation of adhesions by preventing contact between the inflamed pericardium and epicardium, and as the inflammation subsides and the fluid is absorbed, the lining membrane of the epicardium and pericardium becomes more normal so that when the tissues are again finally in apposition, adhesions do not form. Following the use of talc powder and the production of adhesions the presence of blood vessels between the pericardium and epicardium was demonstrated at subsequent operations. Also, microscopic sections of injected specimens demonstrate the presence of blood vessels between these tissues.

It has been shown by many investigators,[9, 10] regardless of whether the graft is muscle, omentum, or pericardium, that the postmortem injection of the vessels in the graft demonstrates that these vessels do communicate with the vessels in the myocardium. We are well aware of the controversy which exists about the value of such communicating vessels,[5] particularly whether an adequate amount of blood is able to pass through these vessels to the ischemic myocardium, and also whether the blood really flows toward the heart or actually away from the heart. Such scientific controversy seems to be of academic interest, particularly when the clinical result is obvious. In other words, regardless of the size of the vessels and regardless of the direction of the blood flow, the patient without the graft is unrelieved while the patient with the graft is relieved, although the scientific question may

still be unanswered. The results are easy to see, although our explanation of how these results occurred, may be at fault.

Following the introduction of the talc powder, a definite inflammatory reaction occurs, involving all of the structures in the mediastinum, the pleura, the pericardium, the epicardium and the adjacent myocardium, the esophagus and the lungs. One of the characteristic features of this inflammatory reaction is the tremendous hyperemia which is produced within a few hours. A fever accompanies this mediastinal reaction, lasting from five to 15 days and gradually subsides. We feel that this hyperemia of the myocardium not only opens up the anastomosing channels between the coronary arteries which are already present, but it also stimulates the formation of new intercoronary channels. Because of the hyperemia, more blood is carried to and is present in the myocardium (just the opposite of myocardial ischemia). This reaction, therefore, is two fold in that it causes a dilatation of the existing vessels with a more efficient supply and distribution to the myocardium, and it also stimulates the formation of new vessels in the myocardium.

As a result of the inefficient lymphatic supply of the pericardium and the large size of the powder particle, very little, if any of the powder, is removed from the pericardial sac. The greater part of the powder remains indefinitely within the pericardial sac, fixed in the adherent tissues. In some instances, it very likely forms talcum powder granulomas and, as such, may persist for many years. Lichtman et al.[6] have recently reported talcum powder granulomas which were present for 10 to 15 years. One of the characteristic features of any granuloma is the hyperemia and the presence of a great number of blood vessels. Again we emphasize the fact that this is exactly the opposite of the ischemic myocardium of coronary artery disease.

By means of animal experiments we were able to demonstrate the ability of the pericardium to furnish a collateral circulation sufficient to overcome the ischemia produced by a sudden, complete ligation of a main branch of the coronary artery, when adhesive pericarditis had been previously established with talc powder.[7]

Discussion

Many questions have been raised as to the disadvantage or possible dangers of adhesive pericarditis. Whether by such an operation for the relief of one disease, another condition might be produced, which in time, would become as serious as the original disease? Whether the presence of an adherent pericardium might interfere with the function of the heart, or make extra work for the heart, thereby resulting in hypertrophy? We believe these questions have been thoroughly and satisfactorily answered and that adhesive pericarditis, per se, in no way interferes with the function of the heart or adds to its work.

It is necessary, at this point, to emphasize the difference between constrictive pericarditis and adhesive pericarditis. The two terms are fre-

quently confused and are often considered to be identical. However, they are entirely different. Constrictive pericarditis may or may not be adherent, and adhesive pericarditis may or may not be constrictive. The procedure which we advocate is the production of an adhesive pericarditis and this is accomplished by the technic described without producing any constriction whatever. This is proved by observations of the venous pressure at varying intervals for over nine years after the operation had been performed. One of the first signs of constrictive pericarditis is an elevation of the venous pressure. This has not occurred in any of our postoperative cases.

The question has also been raised as to whether the adherent pericardium would not become fibrous with the passage of time, and then no longer represent a sufficient source of collateral circulation, or, by reason of a fibrous nature, become scar-like and prevent the passage of blood between the pericardium and the myocardium. From our animal experiments and clinical results, we do not believe that this condition takes place, and in one of our patients who died of congestive failure, three and a half years after the operation, autopsy showed no constriction and the pericardium appeared to be a scaffold for literally innumerable macroscopic blood vessels. There was no evidence of a scar-like tendency on the part of the pericardium. Our first patient has been operated upon more than nine years ago and if such a tendency were going to occur, it seems likely that it would have become manifest within this period of time. Fluoroscopic and kymographic examinations of the postoperative cases reveal the borders of the heart to be mobile and expansile.

In coronary artery disease it is the general belief that nature is constantly producing new collateral channels within the myocardium. Given the necessary length of time or a sufficient stimulus, the rate at which these collateral channels are formed may become equal to or even greater than the rate of occlusion produced by the disease process. When such a situation exists, there is no longer an insufficiency of the coronary supply or a myocardial ischemia.

Almost every operation upon the heart is attended by a certain amount of surgical trauma and inflammation which in turn results in myocardial hyperemia. This hyperemia is the necessary stimulus to the myocardium for the production of its own collateral channels. Even though the acute hyperemia subsides and the immediate stimulus is thereby withdrawn, the increased collateral formation once started may continue for an indefinite period of time. It may well be that this stimulant, which initiates the spontaneous formation of intra-cardiac collaterals, is of greater importance than the formation of the extra-cardiac collaterals.

Selection of Patients

The selection of patients for operation depends upon the following. (1) The establishment of a positive diagnosis of coronary artery disease with

angina. This may depend upon subjective findings such as a distinct and clearly defined anginal syndrome, pain of characteristic nature and distribution with a definite relationship to effort. Or it may depend upon objective evidence of myocardial disease as revealed by the electrocardiogram, although this is occasionally absent. (2) The lack of improvement after fairly prolonged medical treatment. (3) An extreme degree of disability, corresponding to at least class 3 of The Heart Association Classification, necessitating greatly limited physical activities.

A previous coronary occlusion is not a contraindication; however, sufficient time must have elapsed to permit healing of the infarct. The two principal contraindications to operation are congestive failure and an active infarct. An attempt is made to rule out the presence of an active process by means of serial electrocardiograms, blood sedimentation rates and white blood cell counts. These three tests are performed each day for four or five days immediately preceding the operative day. If the electrocardiograms are not stable and the other two tests show an abnormal increase, the operation is postponed.

The pre- and postoperative care, and the postoperative course have been previously described in detail and will not be repeated here.[8]

Operative Technic

The details of the operation have been thoroughly described elsewhere and only the essential features will be mentioned here.[8] They consist of an incision over the fifth left costal cartilage. Approximately two inches of this cartilage are removed leaving the perichondrium. The pericardium is opened for a distance of two inches. Five to 10 minutes before the pericardium is opened the patient receives 5 c.c. of 2 per cent novocaine intravenously to desensitize the myocardium. After opening the pericardium the fluid is aspirated with a soft rubber catheter and the anterior surface of the heart is inspected and palpated for previous infarcts, adhesions and the condition of the descending branch of the left coronary artery. Approximately two drams (by volume) of dry sterile talc powder is spread over the anterior surface, the right and left and inferior borders of the heart. The powder is spread as evenly as possible so that the myocardium is white but the powder is not caked in one spot. The wound edges are protected from the powder by covering them with moist gauze. The pericardium is now loosely and incompletely closed with fine catgut and the soft tissues are closed in anatomical layers.

The novocaine is now used intravenously rather than by topical application on the myocardium. The powder (U.S.P. talc) is prepared by fractional sterilization on three different days preceding the operation and must be dry for easy application at the time of the operation. The operation can be easily performed in less than 30 minutes.

Results

The criterion for the diagnosis as well as for the decision to operate, was the ease with which angina could be produced by effort. In appraising our results, we must naturally consider the relief of pain as of prime importance, although other factors may also contribute to the rehabilitation.

Relief to a patient with angina pectoris means not only relief from the anginal pain but an increased exercise tolerance, for the two are inseparably bound together.

The exact degree of relief or improvement is difficult to measure for several reasons: (1) We have no definite objective test. The nearest approach to an objective test is the exercise tolerance test as done under basal conditions. There are a number of variables in this test so it may not be extremely accurate. (2) The degree of relief is calculated upon a subjective test, namely, relief of the patient's symptoms. The relief of the subjective symptoms is also not an accurate method, but insofar as the patient is concerned it is paramount. (3) The degree of relief may depend upon the presence of other complications such as: (*a*) Subsequent congestive failure which limits exercise tolerance and causes dyspnea, or; (*b*) Hypertension leading to hypertrophy, headaches, dyspnea and a decreased exercise tolerance. No one can predict with complete reliability the degree of rehabilitation insofar as functional activities are concerned, until the patient has actually been tested in those activities and then the degree of rehabilitation may be measured by the ability to perform such activities.

We have attempted to classify the results as follows: Poor means from zero to 33 per cent improvement. Moderate is from 33 to 66 per cent improvement. Marked is from 66 to 100 per cent improvement. The ability to care for their daily needs has been restored to all the patients who are living. With only one exception these patients have been able to return to their former occupations or to engage in other gainful occupations even though many of them had been completely incapacitated before the operation.

Several of these patients have had subsequent attacks of coronary occlusion and some of them have died as a result of the progression of the disease. However, none of the patients who survived for a period of two months after operation died a "sudden death." While this series of cases is too small to assume that "sudden death" may be eliminated by this operation, we do feel that following the operation the possibility of "sudden death" is greatly reduced. The fear of "sudden death" in these patients is sometimes very prominent, and may of itself contribute to the mortality, therefore the relief of this fear is of definite value.

Six patients died in the hospital after operation, giving a hospital mortality of 16 per cent. Three of these patients died within 48 hours of coronary occlusion. Autopsy upon two of them showed infarcts which were apparently present at the time of the operation. The other three patients died within two or three weeks after the operation—two from coronary

occlusion which developed after the operation and one from a rupture through an unhealed infarct which was discovered at the time of the operation. These cases illustrate the extreme degree to which most of our clinical material was handicapped. They also illustrate the difficulty experienced, in spite of our tests, in detecting the presence of an active or unhealed infarct just before operation. Four of the six hospital deaths were in patients who had unhealed and unrecognized infarcts at the time of operation.

TABLE I*

	Number	Per Cent
Total number of operations	36	100
Hospital deaths	6	16
Late deaths up to seven years	5	14
Number of patients disappeared	2	6
Living at present time	23	64

* Since the time this paper was sent for publication, 4 additional patients have been operated upon with no deaths and all with marked improvement.

As can be seen from table 1, there was a total of 36 operations. Excluding the six patients who died in the hospital and one patient who died three weeks after leaving the hospital, and the two patients who could not be followed, we have 27 patients. These patients have been observed from the time of the operation up to the present time or the time of their death. Four of these patients died from one year and five months to six years and 11 months after the operation. Twenty-three are still living and one is nine years after the operation.

TABLE II

Clinical Results

27 patients observed from the time of operation up to nine years or the time of death

Degree of Improvement		Number	Per Cent
Poor	Zero to 33%	4	15
Moderate	33 to 66%	4	15
Marked	66 to 100%	19	70

The results shown in table 2 are based on the criteria which we mentioned earlier and are used to determine the degree of rehabilitation, although the greatest emphasis was placed on the relief of the anginal pain. Seventy per cent were markedly improved and another 15 per cent were moderately improved. According to their own estimates 85 per cent of the patients were more than 50 per cent improved. Eight patients considered themselves to be completely relieved and normal.

The four patients having poor results still have their anginal pain although there is a slight improvement in the exercise tolerance particularly after the use of nitroglycerine. Three of these patients have returned to their former or other gainful occupations. Considering the amount of pathology and the degree of incapacity we believe the results are excellent.

Conclusions

It has been estimated that there were in the United States in 1945 from 800,000 to 1,400,000 patients suffering from coronary artery disease and angina. Many of these patients have restricted physical activities and some are completely incapacitated and are coronary cripples. It is in this last group that we have worked out a program of surgical rehabilitation.

We do not imply that all patients with coronary artery disease and angina should be operated upon. We have operated upon only those patients who were continuing to lose ground after prolonged and repeated medical treatment and who were already incapacitated because of the anginal pain.

The operation which we have described should not be considered as a cure but as a means of surgical rehabilitation for a definite group of patients. It consists in the production of a collateral circulation plus a myocardial hyperemia. The myocardial ischemia is overcome in this manner by extracardiac as well as intra-cardiac collaterals. The operation is simple and requires a small amount of time for its performance.

There are definite criteria as to what constitutes rehabilitation. Eighty-five per cent of the patients were moderately or more than 50 per cent improved and 70 per cent of the patients were markedly or more than 66 per cent improved.

In view of the amount of myocardial pathology and the degree of incapacity, we believe that the results of this form of surgical rehabilitation are excellent.

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PHLEBITIS AND THE DIAGNOSIS OF THROMBO-ANGIITIS OBLITERANS *

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INTRODUCTION

THE making of an early diagnosis in thromboangiitis obliterans is highly desirable. This is true not only because of the serious nature of the malady but also because its progress will usually be arrested if the patient is forced to cease smoking.

At least one-fourth of patients with the disease show an early phlebitis of their veins. This has been known since Buerger described it as "migrating phlebitis," [1] yet the clinician often misses the opportunity to utilize the presence of venous involvement to make an early diagnosis. This report will try to demonstrate that by careful scrutiny of patients with thrombophlebitis, and especially with the help of the biopsy, cases of thromboangiitis may be discovered, and often before there is appreciable involvement of the arteries.

The phlebitis is of interest in late cases as well, both as an aid in establishing an otherwise presumptive diagnosis and as a sign of activity of the disease.

CHARACTERISTICS OF THE PHLEBITIS

1. *The patient is a young person who smokes.* Thromboangiitis obliterans is overwhelmingly a disease of young males. The disease starts in the twenties or thirties. The writer has seen only one patient (Case 5) in whom it began after the age of 40. The patient is invariably a tobacco smoker.[2] Cases in women are extremely rare.

2. *The phlebitis may appear as an idiopathic process or may have a precipitating cause.* Often the phlebitis is initiated by trauma, and the true diagnosis is suspected only through migration of the lesion or its excessively long duration.

3. *The superficial veins are always affected; the deep veins possibly so.* The saphenous vein is most commonly attacked. Involvement of a vessel on the dorsum of the foot, or in the toes, is quite characteristic of the process, since one does not see phlebitis of other causes originating here. Any portion of the superficial veins of either extremity may be implicated. Occasionally, the phlebitis is noted in the external jugular or its tributaries.

It is uncertain how often the deep veins are inflamed in the early stages of the disease to form a part of the migrating phlebitis. That deep phlebitis of small veins is a frequent part of the process is suggested by the oft-occur-

* Received for publication March 12, 1949.
From the Department of Surgery, Tufts College Medical School.
Aided by a grant from the Charlton Research Fund, Tufts College Medical School.

ring deep tenderness, cyanosis, or vasospasm without loss of the pulses. Tender cyanotic toes are frequently seen, and suggest activity in the digital vessels—perhaps of both veins and arteries. Thrombophlebitis of the large, deep veins, such as the femoral, is rare in this type of migrating phlebitis.

4. *The major arteries are ordinarily involved not at all, or only to a minimal degree at the time of a first bout of the phlebitis.*

5. *The phlebitis extends and migrates.* The process typically extends along the superficial veins from its initial focus, both by continuity and by distant involvement of new areas. This accounts for the expression "migrating." The phlebitis does not necessarily skip from one limb to another. It may remain in the initially involved extremity throughout its long duration.

The appearance of the disease in small areas may give rise to the impression that the disease is a dermatologic one.

6. *The process is long lasting and tends to spontaneous reactivation.* A single bout may last weeks, months, or years. At the end of that time, there may still be continued or recurrent inflammation in the original focus, as well as in others. In some patients, recurrent bouts are observed, but they rarely are more than two or three in number.

7. *Pulmonary embolism is rare, except from femoral vein thrombosis.* The author knows of one fatal, and one non-fatal instance, each from an obvious process in the femoral vein. Kahn [3] reports an instance of pulmonary embolism from a phlebitis of the deep veins, and attests to the rarity of this complication.

8. *Biopsy of the vein may reveal a characteristic lesion.* The vessels in thromboangiitis obliterans present three types of pathology: inflammation, thrombosis and intimal proliferation.[4] These processes may occur singly or together. It is only the inflammation which may be said to be characteristic in this disease, though there is no picture which is rigidly pathognomonic.

The inflammation involves all the coats of the vessel, and extends into the perivascular tissue. Lymphocytes, histiocytes, and fibroblasts are prominent; polymorphonuclear leukocytes vary in their number. The elastic laminae are not destroyed, but may be thickened or split ("reduplication"). These findings may be said to be consistent with the diagnosis of thromboangiitis obliterans.

More typical and diagnostic is the presence of an intraluminal granuloma, occurring with or without a thrombus, and made up of the above-named elements plus foreign-body giant cells (figure 1). Though the cells are similar to those of the tubercle, the architecture of the granuloma is not as well ordered as in tuberculosis. Aggregates of cells, similar to those of the granuloma of thromboangiitis obliterans, occur in vessels in other diseases, but are not found within the lumen. Thus, giant cells may be seen about calcific plaques *in the walls* of sclerotic arteries, and in the *media* of the artery in temporal arteritis.

The typical granuloma of thromboangiitis obliterans is found rarely in involved arteries, uncommonly in the deep veins, but with great frequency

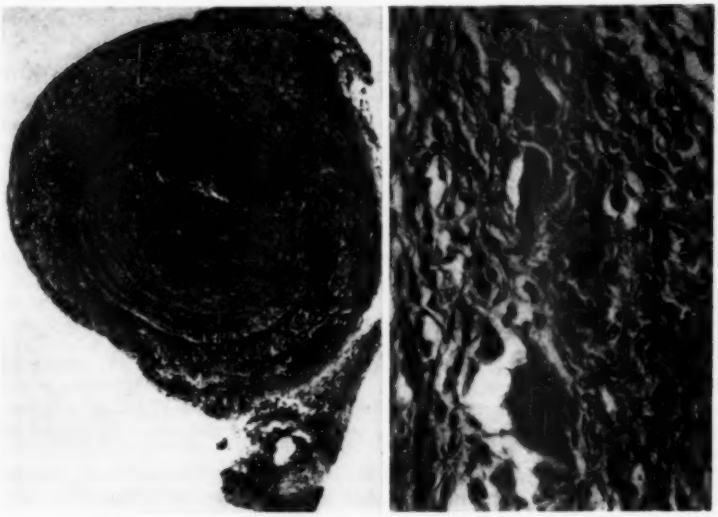

FIG. 1. The characteristic lesion of thromboangiitis obliterans.

Left, section of a saphenous vein involved in a migrating phlebitis. There is marked inflammation, with cellular infiltration throughout the entire vessel, extending to the perivascular tissues. Giant cells are present in the intraluminal granuloma. (Reprinted by permission from New Eng. Jr. Med., 1939, ccxxi, 251.)

Right, detail of the granuloma. (Reprinted by permission from Arch. Path., 1943, xxxv, 241.)

in the superficial veins during the migrating phlebitis. It should be sought for in vessels showing clinical signs of inflammation, and may be found in segments which have been inflamed for months or years.

Biopsy of an inflamed vein is therefore a diagnostic procedure of great value, and involves no special hazard. If the granuloma is found, and if the clinical picture is suggestive, the diagnosis is sure, even when an arterial lesion cannot be found. In the absence of the granuloma, a widespread inflammation of the vein extending to the perivenous tissue is suggestive of the diagnosis, but the author cannot say how much weight should be given to this finding.

MANAGEMENT

Data for the diagnosis of a case of phlebitis of uncertain origin will be obtained from a thorough history and physical examination. The laboratory will aid in uncovering blood dyscrasias. The clinical picture, occasionally aided by a biopsy, will establish the diagnosis of thromboangiitis obliterans. It is worth emphasizing that in the middle-aged patient a migrating phlebitis clinically resembling that of thromboangiitis obliterans has been found in association with visceral carcinoma, especially of the tail or body of the pancreas.[5] In these circumstances, the thrombophlebitis is even more

migratory. Indeed, it is widespread and recurs not once or twice, but many times in quick succession.

Once a diagnosis of thromboangiitis obliterans is established, the patient must immediately stop all use of tobacco. In the absence of ischemia, this may be all that is necessary, and the phlebitis will subside in days or weeks. If the pain and edema of the phlebitis are severe, and especially if there is much vasospasm, sympathectomy has been found to give quite immediate relief. Anti-coagulants or deep vein ligation may be added to the treatment if there is evidence of thrombophlebitis of the popliteal or femoral veins.

Illustrative Case Reports

A. Value of the Biopsy in Early Diagnosis

Case 1. A 26-year-old machinist bruised his right leg at work, setting up a thrombophlebitis of the superficial veins. A segment of inflamed saphenous vein was excised, but the inflammation continued in neighboring veins. When he was seen 11 months after the injury, the phlebitis was still present. Pulsations were present in all the major arteries.

A review of the pathologic slides showed the typical intraluminal granuloma. The phlebitis subsided in a few days after a right lumbar sympathectomy and the cessation of smoking. Three years later, he had mild claudication in the left calf, and had lost the pulsation in the posterior tibial artery. Pulsation returned after a left lumbar sympathectomy. He is now symptom free, eight years after the onset of phlebitis.

Case 2. A 26-year-old mail carrier had suffered a thrombophlebitis of the right saphenous vein after a contusion. When seen two years later, there was continued, active thrombophlebitis of every sizable superficial vein of the right lower limb, from the groin to the ankle. The pulses of the lower extremities were unequal, and there was objective evidence of mild ischemia of the feet.

Biopsy of a superficial vein in the right leg showed the typical picture of thromboangiitis obliterans, including the granuloma. It was learned later that the patient's father had died of Buerger's disease at 38. Bilateral lumbar sympathectomy was performed, and the patient stopped smoking. The phlebitis subsided at once.

Case 3. A 28-year-old shoe salesman presented a thrombophlebitis of the superficial veins of the left lower limb, which had started spontaneously on the foot, and had progressed to the thigh in six weeks. All major arteries showed pulsations of good quality. Biopsy of the saphenous vein showed the widespread inflammation and intraluminal granuloma of thromboangiitis obliterans. The phlebitis subsided two weeks after the patient stopped smoking.

B. Significance of the Phlebitis in Late Cases

Case 4. (Reported through the courtesy of Dr. M. K. Bartlett.) A draftsman of 49 suffered from a phlebitis which started spontaneously on the right foot and ascended to the calf. At the age of 32, he had had a phlebitis of the right calf, initiated by a contusion, and lasting six weeks. At 38, he had a second attack in the left leg and thigh, after a bruise of his ankle, and lasting five months. At the time of his latest and third attack of phlebitis, no pulses were discernible in the left foot. A biopsy of the inflamed vein on the right foot showed the granuloma of thromboangiitis obliterans and finally established the nature of the disease.

Case 5. A shipping clerk began to have claudication at the age of 43. When

first seen, at 49, there were no pulsations below either popliteal level. The onset of symptoms after the age of 40, the absence of a history of phlebitis, and the slow course of his illness led to a probable diagnosis of arteriosclerosis.

At the age of 51, a phlebitis started at the right ankle and dorsum of the foot after a sunburn, and slowly ascended in the leg. Biopsy of the inflamed vein showed the typical granuloma and extensive inflammation of thromboangiitis obliterans, and established the true diagnosis.

Case 6. A 28-year-old laborer had suffered from gangrene of a toe after a crushing injury. The ulceration, amputation, and final healing occupied two years. After this, he was symptom-free for a year. He had not stopped smoking. One month prior to being seen, the right foot became painful and swollen. There was evidence of thrombosis of the popliteal artery, and simultaneously, a thrombosis of the veins of the dorsum of the foot, and of the leg. Biopsy of a vein showed the granuloma and other changes of thromboangiitis obliterans. The limb came to amputation.

In this patient, the appearance of thrombophlebitis coincided with activity of the disease in the arteries.

Conclusions

The presence of a migrating phlebitis of uncertain origin, or of unusual course, may allow a diagnosis of thromboangiitis obliterans to be made before the arteries are involved. Both the clinical characteristics of the phlebitis and its appearance by biopsy are important in establishing the diagnosis.

In later cases, the phlebitis may aid in differentiating the arterial lesion from arteriosclerosis. The phlebitis may also serve as an index of activity of the disease in the arteries, or as a sign that the patient is continuing to smoke.

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RED BLOOD CELL SENSITIVITY IN CAUCASIANS*

By PAUL M. NEUDA, M.D., *New York, N. Y.*

IN a previous paper [1] I had reported that the sickle-inducing substance, the blood-group-enzyme (BGE), which was originally found in feces, was also present in the blood in certain diseases including sickle cell anemia. While, however, the BGE in feces is a normal constituent, the presence of this substance in the blood in disease is apparently an abnormal finding. In the presence of red cell sensitivity, for example, the BGE in blood might be a red cell damaging agent. This could possibly apply as an explanation to sickle cell anemia.

The BGE was, however, not only found in the blood of Negroes but also in the blood of Caucasians. Since "red cell sensitivity to the BGE" presumes the interaction of two factors, the BGE on the one hand, and a preëxisting red cell quality called "sensitivity," on the other, the question arose if there might be present in the Caucasian a pathological red cell figure comparable to the sickle cell of the Negro, and what this figure might be. This question is dealt with in the following study.

The method used in this investigation was that described in my previous papers.[1, 2] Red blood cells, washed three times, were taken up in normal saline to an approximately 5 per cent suspension. As a rule, the blood cells were washed immediately after withdrawal. Traces of these cells were transferred by means of a glass rod into a drop of a BGE-broth produced either from fecal material or from certain bloods. The changes in the red cells appeared after a time interval which varied from a few minutes to several hours. The wide variation in time depended apparently on differences in both the red cell sensitivity and the strength of the BGE. In the sickling blood of the Negro, where red cell sensitivity is extremely high, the cell changes appeared in a few minutes after exposure to the BGE. In other bloods where red cell sensitivity was found low, as in Caucasians, characteristic changes appeared after five to six hours.

Although hundreds of cases have been investigated by this method in the past six years, this study is confined to the material seen between August 1946 and September 1947. During this period, 126 cases were studied of which 76 were Caucasians, 47 were Negroes, 2 were Malaysians and 1 a Puerto Rican.

Before describing the results of this investigation it is necessary to describe in short the typical chain of events which occurs when red cells of a Negro suffering from sickle cell disease are exposed to the action of the BGE.

The development from a normal round cell to the "sickle" does not take

* Received for publication October 21, 1948.
From the Achelis Laboratory, Lenox Hill Hospital, New York.

place in a simple fashion. There are four separate well-defined stages which characterize its development under BGE influence. Each of these stages which occur in succession, represents a complete step in the gradual formation of the "sickle."

It must be emphasized, however, that the BGE does not create any new figures. There is no essential difference in the appearance of the sickle cells produced by the BGE and those produced by anoxia in the sealed wet preparation. However, either because of the specificity of the BGE or its power, the successive changes in the red cells occur with a clarity in the details that are never observed in the simple sealed wet preparation.

The first stage is an enlargement and simultaneous thinning by stretching, of the disc. This picture is in some cases due to the uniformity, of extraordinary beauty.

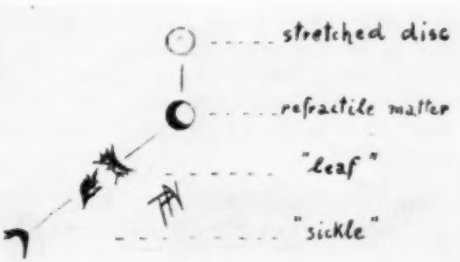

FIG. 1. The four regular stages in the sickle cell development under BGE influence.

The second stage is a striking change in the distribution and appearance of the hemoglobin. There are formed a highly refractile dense area or areas, while the remainder of the cell gets a smooth and paling appearance. Due to the rapidity of the change, stages one and two are often found together.

The third stage is a figure which for convenience because of its characteristic silhouette, may be called "leaf."

The fourth stage is the "sickle" which develops from the "leaf" after it has lost most of its prongs.

These four steps in the sickle cell development * under BGE influence, more precisely in a feces-enzyme-broth, are shown schematically in figure 1.

Although the phenomenon has received its name from the "sickle"-shaped end stage, for reasons which will become later fully clear, the third stage or the "leaf" must be regarded the most significant of all. For the present, it is sufficient to state that the "leaf" is the first sign of actual cell destruction. While stages one and two are reversible, stage three the "leaf," is irreversible. It is of great clinical interest that the sickling process may in some cases exhaust itself with the third stage so that no further development to the

* To be described and discussed more in detail in a subsequent paper.

"sickle" takes place and the "leaf" remains the only sign of the underlying sickling condition.

Of an obvious great significance is the fact that stages one and two are not restricted to Negroes, but can also be seen in Caucasians. Consequently, they are not characteristic of Negro blood as are the "leaf" and the "sickle." There is, however, a red cell figure in the Caucasian, which is as significant of red cell destruction as is the "sickle" of the Negro. It was first observed as an intermediary figure of the sickling phenomenon in the Negro. Though under ordinary conditions, it is only occasionally encountered, it is regularly produced under certain experimental conditions. As described below, when in the mixture of erythrocytes and BGE, plasma plays a major rôle, the development of the "leaf" and the "sickle" is preceded by the appearance of a new figure. This consists of a clear cell fragmentation with the formation of several pieces in "block"-form. This phenomenon may conveniently be called "block"-partition. There is but one interesting difference in this figure as it occurs in the Negro and the Caucasian. In the Negro with sickle cell disease, the several "blocks" resulting from cell partition continue their development to the "leaf" and the "sickle," while in the Caucasian this figure "block"-partition is final. These respective developments are schematically shown in figure 2.

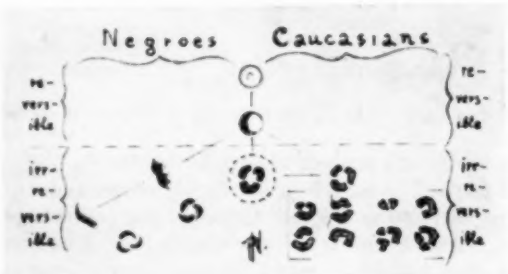

FIG. 2. The red cell sensitivity figures under BGE influence, as they occur in the sickle cell diseased Negro and the Caucasian.

As sickle cell disease does not occur in Caucasians, "block"-partition must be considered as characteristic of an idiopathic condition. This assumption is supported by the fact that "block"-partition as an idiopathic condition, exists also in Negroes not afflicted with sickle cell disease. The partition figure may consist of two, three or more "blocks." In this idiopathic condition, in both Negroes and Caucasians, where separated "blocks" are the remainders of cell destruction, some very characteristic figures are usually seen. They are the figures shown in figure 2 in brackets.

The intermediary "block"-partition figure in sickle cell disease (encircled in figure 2), which may or may not be met in the usual routine investigation, is regularly met, if plasma is added to the reaction between washed red cells

and the BGE. Mere traces of plasma are capable of accomplishing this, as is shown in the following experiment.

Two BGE media, distinct with regard to the plasma content, one a usual feces-enzyme-broth (Schiff), the other a plasma-enzyme-broth (Neuda), were compared with regard to their respective action on the washed cells of a negress (P. G.) suffering from sickle cell disease. Result: the cells suspended in the feces-enzyme-broth, were at the end of 28 minutes transformed directly into "leaves" and "sickles," there was no sign of partition of the cells; the cells suspended in the plasma-enzyme-broth, however, revealed after 34 minutes widespread "block" partition with numerous "leaves" and "sickles" developing from the disconnected parts. Figures 3*a*, a photomicrograph, and 3*b*, a drawing, show block-partition and sickle formation together as obtained in this experiment.

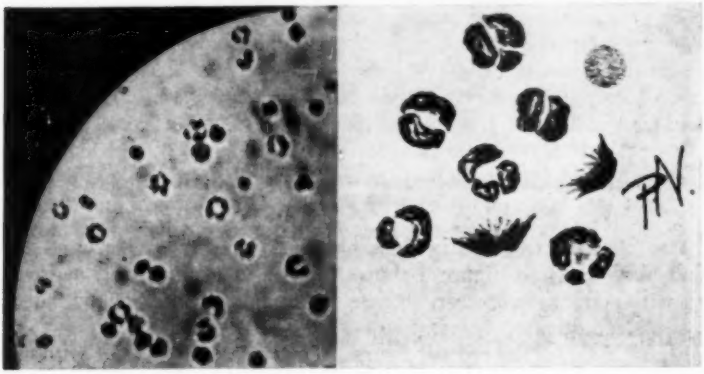

FIG. 3*a*. FIG. 3*b*.

Block-partition and sickle formation together, at left in a photomicrograph, at right in a drawing of selected figures (case F. G.).

This combined BGE-plasma-influence was demonstrated in repeated tests with a plasma-enzyme-broth. It was also reproduced with a feces-enzyme-broth if traces of plasma were added. The influence of the plasma seems to be of a general character and will require further investigation for its elucidation. In these experiments, always plasma of the same blood group was used.

The common occurrence of block-partition as an intermediary figure in sickle cell disease and as an idiopathic figure in both Caucasians and Negroes, in the latter in the absence of sickle cell disease, indicates that this figure very probably belongs to the same type of blood destruction as the "sickle." This is what I had previously termed "hemolysis of sickle cell type."

This concept is supported by the analysis of the 126 cases in this study. Block-partition was found in a significantly higher percentage in the blood

of Negroes than of Caucasians. Of 14 cases, in which block-partition was observed, 11 were Negroes and 3 were Caucasians. Comparing the number of white patients (76) with colored (47), the greater frequency of this form of blood damage in the colored race is obvious: 23.4 per cent of the Negroes and 3.9 per cent of the Caucasians.

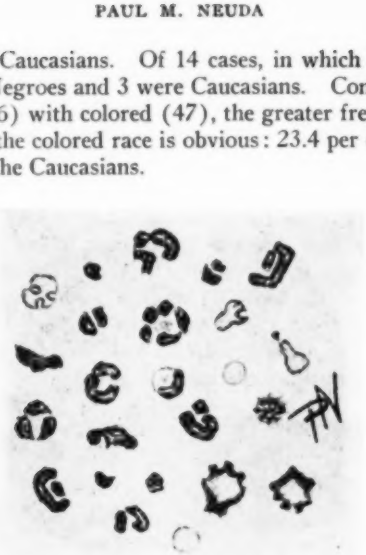

FIG. 4. Selected figures of block-partition in a negress. Washed red cells in a feces-enzyme-broth. Appearance after six hours.

The following two figures show block-partition in a Negro and a Caucasian, respectively. Figure 4 shows the red cell figures in a negress (C. Gu.) with pelvic inflammatory disease and an unexplained anemia, but without sickle cell disease.

Figure 5 shows the red cell figures in a Caucasian (H. K.) with a polyglandular endocrine disturbance. The similarity of these figures with the figures obtained from the blood of the negress, is striking. The "claw"-like forms deserve special mention since they are so characteristic of this type

FIG. 5. Selected figures of block-partition in a Caucasian. Washed red cells in a feces-enzyme-broth. Appearance after five hours.

of blood destruction. They originate apparently by the loss of one "block" in the original circumference of the destroyed cell.

The traceable higher frequency in incidence of block-partition in the colored populace can be explained, at least partly, by the proved intimate connection which exists between this condition and the sickle cell disease. Of the above mentioned 11 Negroes exhibiting block-partition, six were afflicted with sickle cell disease. One might conclude that "hemolysis of sickle cell type" is more widespread in Negroes than in Caucasians. This may actually be so. However, the incidence of this type of hemolysis in Caucasians is not as rare as the above figures would indicate, since there are still other forms of this type of cell damage which can be met as often in Caucasians as in Negroes. A report on these other forms of "hemolysis of sickle cell type" will appear elsewhere.

Of a special interest will be the question, in which diseases can block-partition be expected? On the grounds of the evidence at our disposal, the following can be said. Block-partition tendency of red cells, as revealed by the use of the BGE, is a sign of an inherent liability, called sensitivity. It has, apparently, the same significance as the sickling tendency, though, as a disease, it is of a minor order. As in sickle cell disease, it is frequently found combined with anemia. Unlike sickle cell disease, however, it is not restricted to Negroes but occurs also in Caucasians. In the Negro, the phenomenon is clearly observable only in the absence of the sickling condition, since in its presence, the several blocks rapidly undergo further change to sickles.

The following are the clinical diagnoses in the cases in which block-partition has so far been found: liver disease, especially cirrhosis of the liver, Hodgkin's disease, a malignant ovarian cyst, endocrine disturbances, anemias of undetermined origin and sickle cell disease. Most of the information hitherto obtained on this curious condition, we owe to the sickle cell disease. This makes sickle cell disease a most important object of study for the further elucidation of the mechanism acting in "hemolysis of sickle cell type."

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ELECTROKYMOGRAPHY OF THE HEART AND GREAT VESSELS: PRINCIPLES AND APPLICATION *

By Bert R. Boone, M.D., George F. Ellinger, M.D., F.A.C.P., and Frederick G. Gillick, M.D.

Introduction

The electrokymograph is an instrument which permits the graphic registration of the movements of the heart and great vessels. Many investigators of the cardiodynamics of health and disease have pointed out the importance of studying these movements. Beginning with observations made by the physiologists on the exposed heart, an increasing fund of knowledge has been accumulated. Fluoroscopy, roentgencinematography,[1] and roentgenkymography [2, 3, 4] have all contributed basic information. Each method has definite limitations and only fluoroscopy has wide clinical usage. There is need for methods which can be more easily applied to physiological and clinical usage in intact subjects.

During the past few years several attempts have been made to develop improved graphic methods utilizing the roentgenoscope. These are based on the fact that variations occur in the transmission of x-rays through the heart and/or past its borders as the heart undergoes its phasic volumetric and positional changes. In Heckman's [5] apparatus, these variations in amount of transmitted x-ray are transformed to light variations on the regular fluoroscopic screen. The variations in intensity of light are then picked up by a photo-electric cell which converts them to current changes. Marchal [6] and Hjelmar [7] developed somewhat similar devices. Hjelmar later used a Geiger-Mueller counter, placed directly over the heart, as the sensing device to record x-ray changes. Each of these pick-up and conversion devices was so adapted that variations in current produced in it could be recorded by a galvanometer. Between 1944 and 1947, Henny and Boone, working with the same principle, adapted a modern type photo tube to develop an instrument which they named the electrokymograph.[8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18] Used with the roentgenoscope and electrocardiograph, it produces a permanent tracing—the electrokymogram (EKY), which faithfully reflects the movements and density changes of a chosen portion of the border or body of the heart or great vessels.

This paper summarizes observations made to date, on the electrokymograms of a large group of normal individuals, and indicates some of the significant variations noted in patients with cardiovascular disease. Continued investigations must be made before all the details of the normal va-

* Received for publication March 20, 1948.
From The National Heart Institute, U. S. Public Health Service, Bethesda, Md.

riations can be defined and before it becomes possible to lay down the boundaries between normal and pathological.

The Instrument and Technic

The electrokymograph[8, 9] was specifically designed as an attachment for use with the roentgenoscope and electrocardiograph. When these three units are utilized together, for the purposes of electrokymography, the basic function of each is as follows; the roentgenoscope provides the means for observing the cardiovascular silhouette of a subject and for positioning the electrokymographic pick-up unit over a selected area; the electrokymograph converts the motions and density changes of such selected points to corresponding current variations; and the electrocardiographic galvanometer records these variations on moving bromide paper (an electrokymogram). A carotid sphygmogram is simultaneously recorded for timing and orientation purposes.

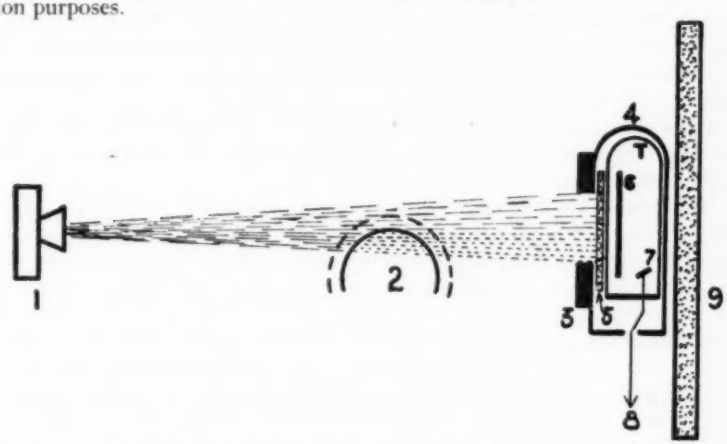

Fig. 1. Schematic illustration demonstrating principles of electrokymograph.
1. Source of roentgen-ray.
2. Heart in systole and diastole.
3. Limiting lead aperture.
4. Copper housing.
5. Small fluorescent screen.
6. Light sensitive surface of photo-multiplier tube (T).
7. Current collecting anode.
8. Connection to galvanometer.
9. Large fluoroscopic screen for general observation.

The electrokymograph consists principally of a roentgen-ray sensitive pick-up unit and its power supply. As shown in figure 1, the pick-up unit is made up of a lead diaphragm (3) with an aperture 5 by 20 mm., which serves to frame or limit the area to be recorded. Behind the diaphragm is placed a piece of fluorescent screen (5) with its light emitting surface close

to and facing the photo-sensitive surface (6) of an RCA 931–A multiplier phototube (T). The pick-up unit is conveniently mounted on the patient side of the ordinary fluoroscopic screen (9) so that both it and the subject's cardiovascular silhouette can be viewed simultaneously. Then as the heart changes in systole and diastole, varying amounts of x-ray activate the small fluorescent screen, producing variations in light. The phototube responds to these light variations and produces corresponding current variations. These current variations are directed into an electrocardiograph * and recorded on moving bromide paper. A rotating mechanism, operated from the fluoroscopist's side of the large screen, provides means of aligning the long axis of the photo-tube aperture parallel to the direction of motion of the cardiac border being examined.

The evaluation and interpretation of the EKY are greatly facilitated by the simultaneous recording of some well-known cardiodynamic event. We find the carotid sphygmogram most satisfactory for routine purposes, though we use the electrocardiogram or stethogram at times. The carotid curve has the advantage of relative simplicity of recording and interpretation and gives a mechanical event to compare with the "mechanical" electrokymogram. Our carotid-pulse recorder [9] utilizes an air conduction system. It consists of a pick-up cup on an adjustable neck clamp, a rubber tube from the cup to the recording mechanism and a recording tambour with a pointer centered in the optical beam of the ECG.

Luisada and Fleischner [19, 20] subsequently reported on the use of the electrokymograph and stethograph and suggested the term fluorocardiography for this method. The term electrokymography has been widely used and has been adopted by two commercial companies † producing instruments for recording cardiac, vessel and other border motions which utilize the principles herein described. Therefore, it would appear confusing to introduce a new term for each combination of an electrokymogram and carotid sphygmogram, electrokymogram and electrocardiogram, or electrokymogram and stethogram. Also, the instrument has been adapted for use other than the study of the heart, for instance, to record the motions of mediastinal masses, as a photo-electric plethysmograph, and more recently as a recorder in ballistocardiography.

Specific instructions may vary for using the Cambridge or the Sanborn electrokymograph. In general the procedure of operation is as follows: the recording galvanometer is turned on and standardized as for electrocardiography. The power supply which energizes the photo-multiplier tube is turned on. The fluoroscope is set at 85 kv. and between 2.5 and 3 ma., and the patient is then placed in position for examination. The carotid-pulse clamp is adjusted to the patient's neck so that an adequate amplitude of carotid-pulse shadow excursion is obtained. The part or parts to be ex-

* While both types of electrocardiographs have been utilized, most of our work has been done with the string galvanometer.

† Cambridge Instrument Company, Inc. and Sanborn Company.

amined are viewed through the fluoroscopic screen and the photo-tube mounting is swung into position, automatically centering the tube in the central beam of the x-ray. By manipulation of the fluoroscopic screen and rotation of the tube, the aperture of the pick-up unit is aligned so its long axis lies parallel to the direction of motion of the part to be studied (figure 2).

As soon as satisfactory alignment is accomplished, the technician introduces the signal into the galvanometer of the ECG by turning the "volume control" of the electrokymograph up slowly. The amplitude of the galvanometer excursions is controlled by this "volume control." The carotid-pulse shadow is again checked. When amplitude and alignment are satisfactory the patient is requested to "stop breathing" in the mid-phase of normal respiration and the ECG camera is started.

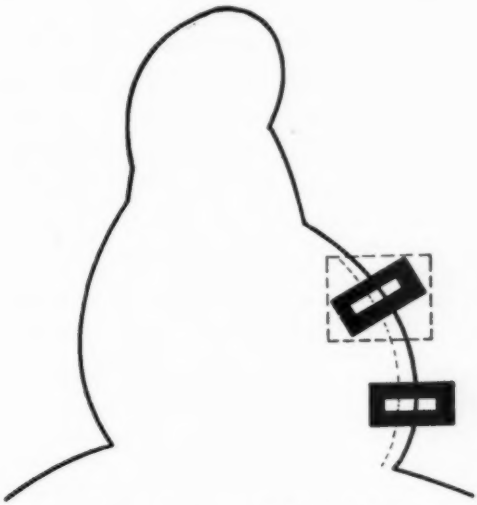

FIG. 2. Illustrating application of aperture of pick-up device over two points on cardiac silhouette. Note long axis parallel to direction of motion of borders, i.e. perpendicular to border. Moving shadow remains within aperture. After proper alignment of pick-up device, roentgen beam is coned by roentgenoscopic shutters (dashed square).

While no standard patient positions or views have been established for "routine" electrokymographic examination of the heart, the following segments of the cardiovascular silhouette have been examined in most instances: (1) Posterior-anterior projection; left ventricle (lower, middle, and upper), pulmonary artery, aortic knob, right atrium. (2) Right-anterior-oblique projection; left ventricle (lower and middle), pulmonary artery (when not obtained in posterior-anterior projection) and dorsally the areas of the right and left atriae. (3) Left anterior-oblique projection; left ventricle (lower and middle), left atrium, ascending aorta, right ventricle.

The posterior-anterior projections are routinely used. When using the oblique projections, the subject is rotated to whatever degree necessary to bring a desired chamber or vessel into silhouette. As is well known, there is wide individual variation in the cardiovascular silhouette of normal subjects and in the presence of cardiovascular disease. Therefore, the patient position and the precise degree of rotation needed to examine a particular chamber or vessel will vary.

The time required to complete an EKY will depend upon the speed and teamwork of the fluoroscopist and technician and on the number and length of records taken. Our average examination includes about 12 records and requires less than 10 minutes. Exposure to radiation during such a "routine" EKY amounts to less than five minutes. This amount of radiation under our conditions of operation is well within the margins of safety.

Normal Electrokymograms

This report is based primarily on the study of electrokymograms of 140 medical students and nurses, age 17 to 32, who had no clinical evidence of cardiovascular disease. The entire group had two electrokymographic examinations done two to three months apart and in some instances a third examination. In addition, a smaller number of normal persons of intermediate age, a large group of older men and selected subjects with cardiovascular disease have been examined. Altogether approximately 500 subject examinations have been made in the past two years.

Certain physical characteristics, common to all electrokymograms, should be pointed out before discussing the records from specific chambers or vessels. All can be studied as to their configuration, amplitude and timing. A study of configuration shows that electrokymograms are made up of ascending and descending limbs, peaks, plateaus and other complexes. The electrokymograph is so connected to the galvanometer that a descending limb results from the medial movement of a particular border, a decrease in density of a part, or any combination of these changes which allows increased transmission of x-rays. An ascending limb results from lateral movement of a border, an increase in density, or any combination of these changes which decreases the transmission of x-rays. A rapid change in density or border movement produces a steeply sloped limb, while slow changes produce more gradual slopes. When a part is not moving or changing density, or when complex movement and density changes exactly counteract one another, a straight line is recorded. Peaks, domes, notches, etc. result from changes and shifts in balance of border movement and density, which occur as the heart undergoes volumetric, positional or shape changes during its cycle of activity.

A method of standardizing amplitude has yet to be perfected. At present the operator determines the amplitude of the curve by altering the volume control setting. Arbitrarily the amplitude is set so that it is approximately

equal to the cycle length in millimeters which gives a record with good characteristics for reading. The amount of motion at two points can be compared by taking records with the identical setting of the volume control. This gives an approximation of the relative amount of motion but the curves do not represent quantitatively the amount of movement. When recording from one point of the silhouette, variations in amplitude at a constant volume setting are significant. Another point to be remembered is that the instrument registers only that component of border movement which occurs at an angle to the axis of the central x-ray beam. When the movement is at a right angle, the greatest amplitude will be recorded. Movements in the same axis as the beam register only when they are accompanied by density changes of the part. These density and movement changes may then merge with or neutralize one another and thus alter the amplitude of the EKY.

The timing of the curves can be accurately determined. Time lines on the record are the same as for electrocardiography, i.e. each small space $= 0.04$ sec. We believe the records can be read with an accuracy of ± 0.01 sec.

Many observations presented here substantiate and some differ from those made previously with the roentgenkymograph and other instruments. No attempt will be made to give individual credit to the many workers who contributed the remarkable fund of basic data on which we have drawn freely.

The Ventricular EKY. The left and right ventricular electrokymograms have basically similar configurations, though they may differ in detail. Each cycle consists of a major descending limb due essentially to the medial movement of the ventricular border during systole, and an ascending limb associated with lateral movement of the wall in diastole. Superimposed upon these two basic limbs are peaks, plateaus, and other variants. The records are surprisingly similar to volumetric curves of the ventricle obtained by direct cardiometer methods in animal experimentation.[21] Though they reflect volumetric changes to a remarkable degree, they also show effects from pendulum movement, rotation and shape changes of the heart.

The interpretation of the EKY from the carotid sphygmogram has been previously described.[16] The onset of the major ascending limb and the cleft of the incisura on the carotid curve are identified. Projection from these points to the EKY helps to identify the onset of ventricular ejection and the onset of isometric relaxation respectively. In many records the onset of the descending limb of the incisura is well defined and identifies the beginning of protodiastole; in some, ventricular isometric contraction is registered on the pulse wave. Starting from these points, the application of known facts concerning the phases of the cardiac cycle permits completion of the analysis.

When studying a right ventricular record, it is best compared with another right heart event, the pulmonary artery EKY. Since these are not simultaneously recorded, the carotid sphygmogram is used as a common time reference curve. A convenient method is to make a tracing on trans-

parent paper * of the EKY of the pulmonary artery. A vertical line is drawn on this tracing through the ejection point of the accompanying carotid curve. This transparency is then superimposed over a right ventricular record so that the vertical mark is aligned with the ejection point of the carotid sphygmogram which accompanies the ventricular EKY. When cycles of equal length are chosen, this method greatly facilitates the comparison of the activities of various chambers and the study of the effect of the activities of one chamber upon another. Simultaneous recordings of the stethograph or some other cardiodynamic event are used to help complete or substantiate the analysis when necessary.

Two lag factors must be taken into account when making the projection from the carotid pulse wave to the EKY: (1) The passage of the carotid pulse wave from the neck through the recording apparatus takes 0.01 sec.; (2) Passage of the pulse wave from the root of the aorta to the carotid artery takes 0.01 to 0.03 sec. (ave. 0.013). This latter can be determined for any individual from the ascending aorta EKY and its simultaneously recorded carotid pulse wave. A third possible lag factor appears in some instances where movement of the ascending aorta follows that of the left ventricular wall by 0.01 to 0.02 sec., but this matter requires further study. In the average record, a total lag of 0.03 to 0.04 sec. is used when studying ventricular curves.

Figure 3 schematically illustrates the most common type of ventricular curve (A), with some normal variations (C, D, E). Using the carotid sphygmogram (B), the interpretation can be made in terms of the physiological phases of the cardiac cycle as defined by Wiggers and others.

Isometric Contraction Phase (1–2): During this phase the ventricle is a closed chamber undergoing no volumetric change. However, it is changing from an ellipsoidal to a more globular shape,[22] thus producing a positional change of the border. The direction of movement depends on the point at which the record is taken and on the balance of factors affecting the movement of the particular segment. It is usually a descending limb in the PA projection, but may be ascending or horizontal. At times it is not demarcated, but merges with the ejection limb. The duration of this phase, as determined on the EKY, approximates previous estimates of 0.04 to 0.06 sec.

Ejection Phase (2–3): Following the opening of the semilunar valves at point 2, the ventricular wall, in most instances, moves outward for approximately 0.02 to 0.03 sec. This is believed due to a positional shift of the border as the a–v septum starts toward the apex and the latter rotates. Then, at point "x", the medial movement due to decrease in ventricular volume predominates and the major ejection limb is inscribed as a rapidly descending complex. The early positional change may not be evident when it merges with the isometric contraction movement or other complexes as in

* "Traceolene" paper as manufactured by the Transolene Company, Barrington, Illinois, has proved particularly suitable for this purpose.

figures 3-D and E. The terminal portion of the ejection wave slopes more gradually and its end point is not definite in all curves. It is of interest to note that Wiggers [21] has observed a peak similar to that marked "x" in volumetric curves, which he called an "accidental" wave. In our records it appears to represent a shift in balance between positional and volumetric factors affecting border movement.

Protodiastolic Phase (3–4): This is the least clearly demarcated phase of the cardiac cycle on an EKY. It is approximately 0.04 sec. in duration and is a slightly concave descending segment. Its onset usually merges smoothly

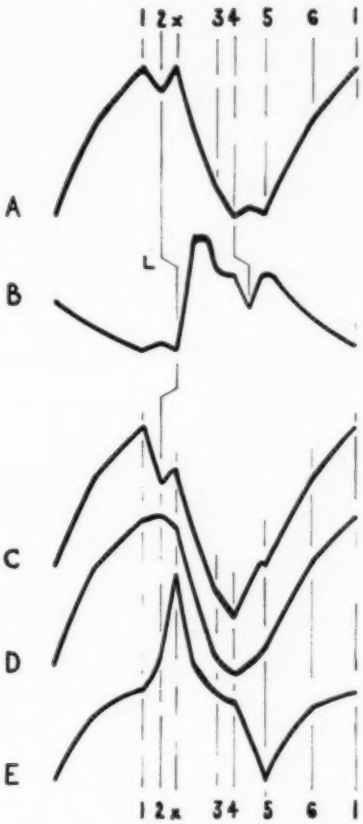

FIG. 3. Schematic drawing illustrating method of interpretation.

A, C, D, E—Variations of left ventricular electrokymograms, normal subjects. B—Carotid sphygmogram. L—Correction factor for lag of carotid recording system and pulse wave transmission time (see text). Vertical lines indicate phases of cardiac cycle.

with the terminal portion of the ejection limb, while its end point ordinarily is marked by abrupt angulation of the curve. Wiggers has identified this brief phase as that interval between the end of systolic ejection and the closure of the semi-lunar valves. As such, it is the first interval of diastole and does not refer to the same portion of the cardiac cycle as when the term is used clinically.

Isometric Relaxation (4–5): During this period the ventricles are again closed chambers and no volumetric change occurs. The complex which follows aortic valve closure at point 4, varies considerably. Commonly it resembles, and is opposite in direction to that of isometric contraction. It may be ascending (3C and D), biphasic (3A), or descending (3E). The latter is more common in the oblique projections. The movement is believed due to positional shifts of the ventricle as it returns to its resting state. Its duration varies from 0.06 to 0.16 sec.

Ventricular Filling (5–6, 6–1): The ventricle fills rapidly in early diastole producing a sharply ascending limb (5–6). With the decreasing rate of filling a change in slope occurs in later diastole (6–1). When the pulse rate is slow, evidence of auricular systole is occasionally seen. The duration of ventricular filling varies with pulse rate though no detailed studies of this relationship have been done.

Figure 4 shows examples of normal left ventricular curves comparable to those schematically shown in figure 3. In this and all subsequent examples, the upper record is the EKY, the lower is the carotid sphygmogram. Variations of A, B, and C are the usual curves of the middle and lower left ventricle in the posterior-anterior projection. While a certain type of curve may be most common in one segment of the heart, or in one projection, there is considerable variation. Such factors as the shape of the heart, height of the diaphragm, position of the patient, etc. affect the curves and account for patient to patient differences or differences on reëxamination of the same patient. Records such as D are rarely obtained except in certain oblique projections.

The ventricular EKY appears to provide an opportunity for measuring, on a single curve, more phases of the cardiac cycle than has been previously possible. However, changes in direction or in steepness of slope of a limb do not always coincide with the onset of a specific event of the cardiac cycle; nor does the onset of a specific event always produce a definitely demarcated change in the EKY. The factors affecting border movement are so complex that the motion of any particular point on the heart border cannot be completely coördinated with events of the cardiac cycle. The EKY is a record of the net effect of all factors effecting transmission of x-ray.

A number of examinations have been made with the patient recumbent. Generally, they reveal a smoothing out of the entire curve so that it assumes a more trapezoid form (figure 5). The early systolic and diastolic changes are not so evident and the slow filling phase of diastole produces a horizontal or descending plateau. These differences appear due to the altered ana-

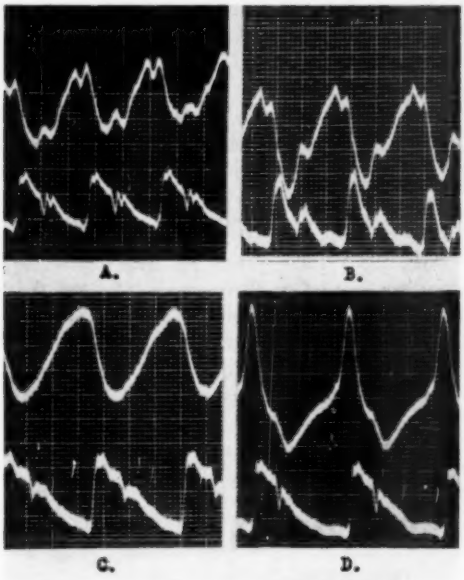

FIG. 4. Left ventricular electrokymograms showing variations in normal subjects.

In this, and subsequent illustrations, the upper curve is the EKY and the lower curve is the carotid sphygmogram.

A—PA projection, left lower border. B—Same projection, middle left border. C—LAO (20°), middle left border. D—LAO (60°), lower left border.

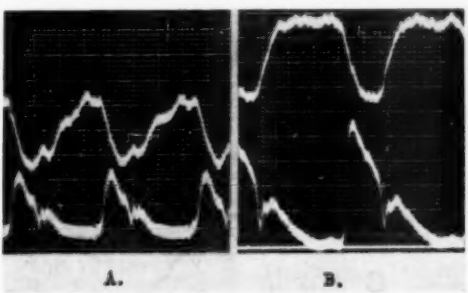

FIG. 5. A—EKY, middle left border, left ventricle (PA). Subject standing.
B—Same with subject recumbent.

tomical relationship of the heart within the thorax, the slower heart rate and the increased ventricular filling which occur in the recumbent position. It has been noted that at rapid heart rates the ventricular curves may assume a more spiked contour.

It should also be noted that the highest and lowest points on the EKY do not necessarily represent the position of the border at the onset of systole and diastole. Though they represent the farthest lateral and medial movement of the ventricular wall, part of this movement may be due to positional change. This is well illustrated in figures 3E and 4D, where the highest peak occurs well after the onset of systole and the lowest peak after the onset of diastole, i.e. at the end of isometric ventricular relaxation.

Atrial Electrokymograms

Each cycle of the EKY taken from the areas of the atriae, usually consists of a basic pattern of two or three waves (figures 6 and 7). Considerable variation can occur in their details. Many resemble jugular phlebograms, but the same interpretation cannot be applied to both because they result from different mechanical factors. The atrial wall may move as a result of intrinsic atrial activity, because of transmitted motion from adjacent structures, or as part of a movement of the heart as a whole. Since the atriae are thin-walled and relatively inactive chambers riding on vigorously active ventricles, transmitted motions from the latter or from adjacent

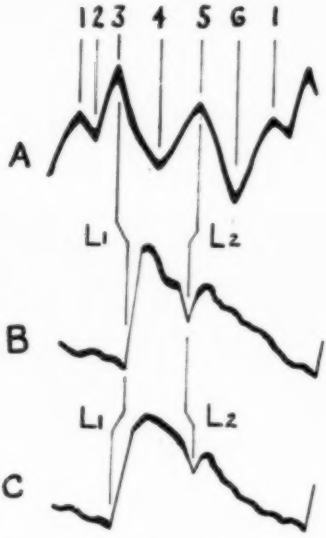

Fig. 6. Schematic basis for interpretation, right atrial EKY.

A—EKY, right atrium (mid position, PA). B—Carotid sphygmogram. C—EKY, pulmonary artery. Two steps: (1) comparison pulmonary and carotid artery, (2) comparison carotid to right atrium. L_1 and L_2 indicate time differences between opening and closing of semi-lunar valves on carotid and pulmonary artery records. For further detail see text.

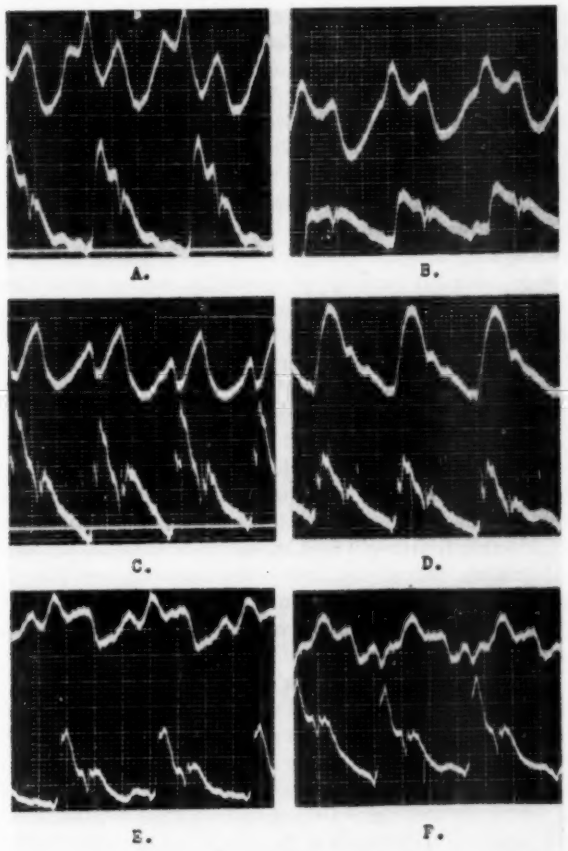

FIG. 7. Atrial electrokymograms illustrating variations in normal subjects.
A, B, C—Right atrium, PA projection. D—Pulmonary artery EKY, subject C, for correlation. E, F—Left atrium, RAO and LAO respectively.

arteries may dominate the curve. The effect of these and other physiological factors may vary from patient to patient, on the right and left atrium, or on different segments of the same atrium. For example, a recording from the right atrium close to the cardio-phrenic angle, may show predominately ventricular type movements; near the middle of this chamber silhouette, the ventricular effects are less marked and more evidence of intrinsic atrial activity may be seen; along the upper segment, the movements of the ascending aorta and/or superior vena cava may modify the curve. These varying influences may produce changes in contour of the record which mask or

modify those produced by the events of the atrial cycle. Each record must be individually analyzed as to what factors produce any specific movement. The superimposition of transparent tracings from different chambers is very helpful in this analysis.

For routine purposes, the carotid sphygmogram is preferred as a basis for interpretation of atrial curves. The right atrial EKY, however, cannot be directly compared with the carotid curve, since similar events on the two sides of the heart are not always synchronous. Therefore, the pulmonary artery EKY is utilized as shown in figure 6. The atrial and pulmonary artery electrokymograms are obtained separately in ordinary work. The simultaneously recorded carotid sphygmogram serves as a common time reference curve. The first step in interpretation is (a) the determination of the interval between the onset of the ejection wave on the carotid sphygmogram and that on the pulmonary artery EKY (L_1 of figure 6); and (b) the determination of the interval between the nadir of the incisura of these two records (L_2). Step two is the application of these relationships to the atrial curve. On figure 6, L_1 and L_2 are shown of differing duration and direction. The time relationship between the onset of the ejection wave on the carotid sphygmogram and that on the pulmonary artery EKY is not necessarily the same as the relationship between the incisura on the two curves since the duration of ejection from right and left ventricle may vary (Katz).[23] The right atrial and the pulmonary artery electrokymograms can be recorded simultaneously, but this requires additional special apparatus. The interpretation of the right atrial EKY, shown in curve A, figure 6, can be made as follows:

1–2: This first negative limb represents movement of the atrial wall toward the mid-line and is associated with atrial systole. In the two-waved atrial curves (figures 7, B and C), it may be absent or may be evident only as a poorly defined change in contour.

2–3: The first positive wave represents an outward movement associated with early ventricular systole and related to a-v valve closure. It is probably due in most instances to pressure or positional changes transmitted from the ventricle during its isometric contraction phase. It is present on both two and three-waved curves.

3–4: The second negative wave is associated with ventricular ejection and is believed due to the descent of the atrio-ventricular septum toward the apex. This pulls the atrial wall sharply toward the mid-line; at the same time the atrium rides inward on the ventricle as the latter becomes smaller. In most cases point 3 corresponds to point "x" of the ventricular record (figure 3). In some instances ventricular ejection begins at point 3. The wave may then descend to the baseline or only a short way, dependent upon the degree of ventricular effect on the curve.

4–5: The second positive wave begins at about the middle of the ventricular ejection period. Apparently at point 4, atrial filling becomes the

dominant factor and produces an outward movement despite the fact that the ventricle is still getting smaller. The V or L-shaped complex, 3–5, is quite consistently present and is often the largest complex of the right atrial EKY.

5–6: The third negative limb begins with the closure of the semi-lunar valves at 5 and ends with the opening of the a-v valves at 6. This movement is believed due to a positional shift of the heart as a whole. This can be shown in some cases by comparing movement of right and left heart borders. The depth of this limb varies, but it is clearly present in most records. Its duration is the same as that of the isometric ventricular relaxation phase as measured on the ventricular EKY. In some instances the complexes from 4 to 1 bear a different time relationship to the incisura of the arterial curves so that the semi-lunar valves appear to close between 4 and 5, and the a-v valves open at point 5. In such cases, the identification and interpretation of these complexes varies from that of the usual curve just described.

6–1: The third and final limb is correlated with the onset of ventricular filling. It might be expected that the atrial wall would move inward as blood passes from atrium to ventricle. During this period, however, the atrium rides outward on the expanding ventricle and apparently the column of blood in atrium and vein moves "en masse" so that very little intrinsic movement of the atrial wall occurs until its systole begins.

Right atrial curves were easily obtained in most subjects at approximately the middle of the right lower arc of the heart, with the subject erect and in the PA projection. Occasionally the right ventricle formed this segment of the silhouette. In the recumbent position, a predominately arterial or ventricular type wave was usually seen in this area.

The carotid sphygmogram is used directly to aid in the interpretation of the left atrial EKY. Referring to figure 6 and figure 7F, the movements of the left atrium between points 1 and 4 are similar to the movements of the right atrium. Between points 4 and 1, the curves usually differ, in that on the left atrium the semi-lunar valves appear to close between 4 and 5, while the a-v valves open at point 5. Phillips,* and Luisada,[19] using the stethogram for orientation, reached a similar interpretation. In our experience it has been hard to obtain "pure" left atrial electrokymograms in normal subjects. It is difficult to be certain that this chamber is in silhouette and to visualize it free from adjacent structures in the various oblique projections. Even when the silhouette seems well visualized, the curves obtained often show predominantly ventricular, arterial or "mixed" characteristics.

In summary, it is emphasized that factors affecting atrial border movement are quite complex and at the moment we feel much as F. Roberts,[24] that the atriae, to a great extent, are passengers in the movements of the ventricles, making it difficult to distinguish between active and passive atrial movement.

* Personal communication from Dr. Edward Phillips, Peter Bent Brigham Hospital, Boston, Massachusetts.

Arterial Electrokymograms

Electrokymograms from the pulmonary artery, ascending aorta and aortic knob closely resemble the carotid sphygmogram (figure 8). They can be described with reference to the phases of the ventricular cycle.

The onset of ventricular systole (isometric contraction) is usually not reflected in any clear cut change on the arterial EKY. In some instances, a small wave, either negative or positive, appears 0.04 to 0.06 sec. ahead of the major upward limb. Such a "preëjection" complex, when present, is probably due to positional change of the vessel or pressure change transmitted through the semi-lunar valves, occurring as the ventricle alters shape and intra-ventricular pressure increases during isometric contraction.

The onset of ventricular ejection results in a sharp upward movement of the tracing which reaches its peak near mid-systole. As ejection pro-

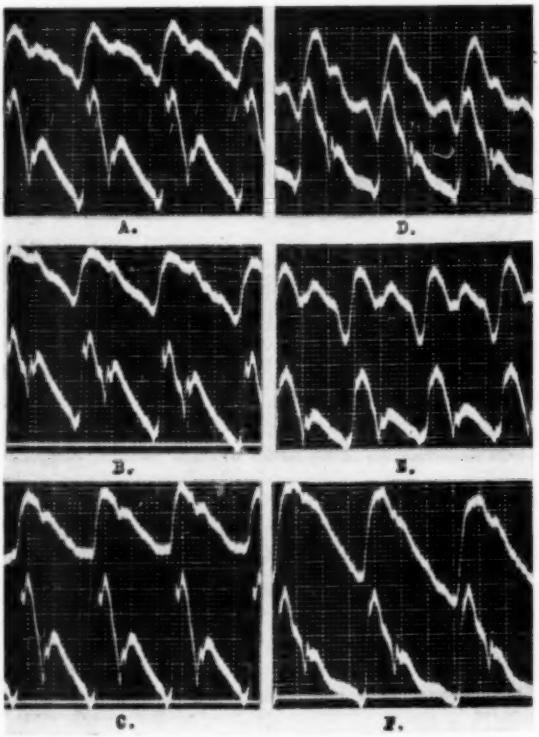

Fig. 8. Arterial electrokymograms, normal subjects.

A, B, C—Pulmonary artery, ascending aorta, and aortic knob, subject N. H. D, E, F—Pulmonary artery, ascending and aortic knob, subject J. S.

ceeds, a descending limb of lesser slope is inscribed. The end of the ventricular ejection phase is marked by a break in contour, or an incisura on the descending limb though not as definitely as on the carotid sphygmogram. The protodiastolic phase of ventricular activity is also not always clearly defined. The onset of ventricular diastole (isometric relaxation) is marked by a small upright wave which gives way to a gradually falling slope. This may be smooth in its descent or may show irregular undulations and peaks.

Electrokymograms from the aortic knob generally show an abrupt, steep, rising limb, a peaked contour, an "incisura" at a high level above the baseline, and a descending limb of lesser slope. In comparison with this, the pulmonary artery curves tend to show rising and falling limbs of more equal slope, a more rounded contour and "incisura" falling closer to the baseline. The electrokymograms of the ascending aorta are variable in appearance and in many instances show a large secondary wave after the incisura, figure 8E. This appears related to superior vena cava activity and probably represents an "impure" curve with both ascending aorta and superior vena cava in the recording aperture. Variations from these generalities are common so that it is not possible to identify a curve as pulmonary artery, ascending aorta, or aortic knob from its appearance alone. From rough comparisons, aortic curves appear of greater amplitude than pulmonary artery records, though standardization of height is not possible at present.

The technic of obtaining these records varies with the individual patient. In normal young adults it is easy to record the aortic knob movement in the posterior-anterior projection. Occasionally the knob may be inconspicuous and a slight degree of rotation may be needed to bring it out. The pulmonary artery tracings are usually obtained in the posterior-anterior projection, though at times it is necessary to rotate the subject into the right anterior oblique position. This is especially true in subjects with a transverse type heart. Electrokymograms of the ascending aorta are taken close to the point of origin of the vessel and are most easily obtained with the subject in the LAO position. The optimum degree of rotation varies. As indicated before, the right border of the ascending aorta cannot always be thrown into silhouette free from the superior vena cava and the spine shadows. We have had difficulty in visualizing and recording the movement of the descending aorta below the aortic knob. Among subjects over 60 years of age, satisfactory arterial curves have not been obtained as easily as in younger subjects. A dilated or tortuous descending aorta or enlarged left ventricle, for example, may interfere with visualization of the pulmonary artery. Where, as in older subjects, the descending aorta forms a distinctly visible arc to the left of the spine its movements can usually be recorded. For movement to be recorded in this area, it appears that (a) the density of the vessel must be increased so as to give contrast with surrounding structures; (b) the vessel must be curved enough so that the passage of the pulse wave can produce a positional shift. Our work so far leads to the belief

that the recorded movements of the great vessels are due more to straightening and positional shifts of the vessel associated with the passage of the pulse wave, than to true expansile pulsation.

A number of interesting and valuable measurements have been made from the arterial electrokymograms recorded simultaneously with the carotid sphygmogram. One of our first applications has been to study the synchronism or asynchronism of ventricular ejection in normal subjects, and in patients with bundle-branch block.[17] The method is based on the determination of the time interval between the onset of the ejection wave on the pulmonary artery EKY and that of the ascending aorta EKY. For practical purposes, this indicates the time of onset of ejection of blood from the right ventricle relative to that from the left ventricle. This time can be determined by recording pulmonary artery and ascending aorta separately, each with a simultaneous carotid sphygmogram, then using the latter as a common time reference curve to compare pulmonary artery and ascending aorta. The electrokymograms of the pulmonary artery and ascending aorta can also be recorded simultaneously. This is more difficult and time consuming and requires a special multiple channel instrument.

TABLE I

AAc		AKc		AAc to AKc Difference		PAc		PAc to AAc Difference	
Sec.	No. Subj.	Sec.	No. Subj.	Sec.	No. Subj.	Sec.	No. Subj.	Sec.	No. Subj.
.00	9	.01	21	.03	5	03	16	.03	2
.01	34	.00	46	.02	26	.02	20	.02	6
.02	19	−.01	31	.01	28	.01	32	.01	13
.03	6			.00	8	.00	14	.00	14
						−.01	18	−.01	19
								−.02	11
								−.03	3
Aver. .013		.01 to −.01		.014		.03 to −.01		.03 to −.03	
Total Subj.	68		98		67		100		68

The measurements studied to date are listed in table 1. AAc, PAc, and AKc denote the interval between the onset of ejection on the ascending aorta, pulmonary artery, and aortic knob electrokymograms and the onset of ejection on the simultaneously recorded carotid sphygmogram.

Column 1: The AAc measurement indicates the pulse wave transmission time between the ascending aorta and the carotid. In the normal young subjects it ranged from 0.00 to 0.03 sec. (average 0.013). It is probable that the 0.00 readings actually represent values between that figure and 0.01 sec. since the method is accurate only within 0.01 sec. In addition, positional shifts of the aorta may occur with ventricular activities and obscure or alter the apparent take-off point of the aortic ejection wave.

Column II: The AKc measurement indicates the difference in the time of arrival of the pulse wave at the aortic knob and the carotid artery. It varies from + 0.01 sec. to — 0.01 sec., i.e. the onset of "ejection" on the aortic knob EKY may coincide with, or may precede or follow that on the carotid sphygmogram by as much as 0.01 sec. This variation can be explained by (1) differences in the distance from the left ventricle to the two points of recording; (2) differences in rate of pulse wave transmission from the aorta to the points of recording. A preliminary study of a large group of older men, most of whom had some degree of aortic arteriosclerosis with elongation and tortuosity, has shown a significant number of subjects in whom the aortic knob ejection point occurs as much as 0.05 sec. after the carotid ejection point.

Column III: AAc to AKc difference. This measurement indicates the time for transmission of the pulse wave from the ascending aorta to the aortic knob. It varied from 0.00 to 0.03 sec. (average 0.014 sec.). Again the 0.00 readings probably represent values between that figure and 0.01 sec. This value is prolonged in many older subjects.

In the living subject the distance from the point of recording on the ascending aorta to that point visualized as the "aortic knob" is variable. It can be estimated at 8 to 10 cm. from measurements given in anatomy text books.[25] Assuming that AAc to AKc times of 0.00 are actually 0.01 sec., the transmission time from the ascending aorta to the aortic knob becomes 0.01 to 0.03 sec. Then the pulse wave transmission rates in the aorta would be from 3 to 10 meters per second. This closely approximates prior estimates.[26]

Column IV: The PAc measurement indicates the difference in the time of onset of the ejection waves on the pulmonary artery EKY and that on the carotid sphygmogram. It serves to compare right and left heart events. It varied from + 0.03 to — 0.01 sec., i.e. pulmonary artery ejection might precede carotid ejection by as much as 0.03 sec., or follow it by as much as 0.01 sec. The range of the PAc measurement is sufficiently narrow and constant that unusual variations can be considered as indicative of abnormal degrees of ventricular asynchronism. In a large group of normal adults all measurements were between + 0.03 and — 0.01. In 15 of 16 patients with bundle-branch block, measurements were significantly outside this range (LBBB 0.04 to 0.07 and RBBB — 0.04 to — 0.05 sec.).[17] Since this previous communication, we have examined a group of subjects over age 60, and to date their PAc measurements have corresponded to those of the younger age group except in two of 30 cases. One of the exceptions had a dilated descending aorta which may have been superimposed on the pulmonary artery.

Column V: PAc to AAc difference. This measurement can be used to determine the actual degree of asynchronism of ejection from right and left ventricles.[17] In normal subjects it was found that the PAc to AAc difference equals + 0.03 to — 0.03 sec., i.e. the ejection on the pulmonary artery EKY

might precede or follow that on the ascending aorta by 0.03 sec. Stated differently, ejection from either ventricle may precede that from the other by as much as 0.03 sec. In a group of 68 normal subjects left ventricular ejection led in 33 cases; right ventricular ejection led in 21 cases; ejection was synchronous in 14 cases. On reëxamination of a number of these subjects, the PAc and AAc times were found in the same range, and individual measurements, with rare exception, were within 0.01 sec. of the original. This resulted, in an occasional case, in a change of the degree or side of asynchronism. We have observed this same phenomenon of changing asynchronism while making a continuous recording as a subject held his breath for a long period. Thus far, we have found PAc to AAc differences greater than 0.03 sec. only in subjects with electrocardiographic evidence of bundle-branch block. The results in the normal group differ from those of Luisada and Fleischner [20] who found, in eight cases, that right ventricular ejection always led.

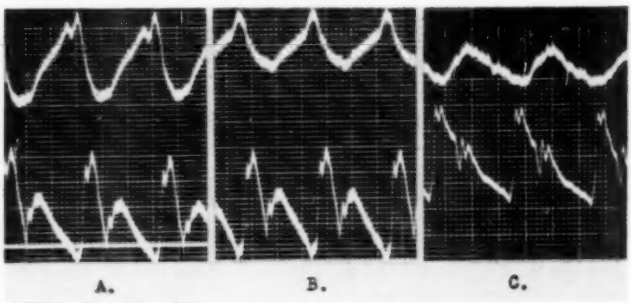

FIG. 9. Miscellaneous electrokymograms.

A— Left ventricle, middle left border (PA). B—Density, same subject, taken 2 cm. medial from border. C—Density curve from right lower lung, normal subject.

These measurements are accurate within about 0.01 sec. We have recorded simultaneously from similar levels on right and left carotid arteries, and find no difference in timing of the complexes, so that either vessel can be used for electrokymographic work. It would be expected that pulse wave transmission time in these vessels would vary with changes in blood pressure, pulse pressure, etc. Under the conditions of our examination, no appreciable change in these factors was noted, except for lessening of tachycardia in some excitable subjects as the examination progressed. In some instances blood pressures were taken before, during and after the examination. Such changes as appeared did not alter the blood pressure beyond the normal range and the various electrokymographic measurements were not significantly changed. The effects of greater pulse rate and blood pressure variations on electrokymographic measurements are in process of study.

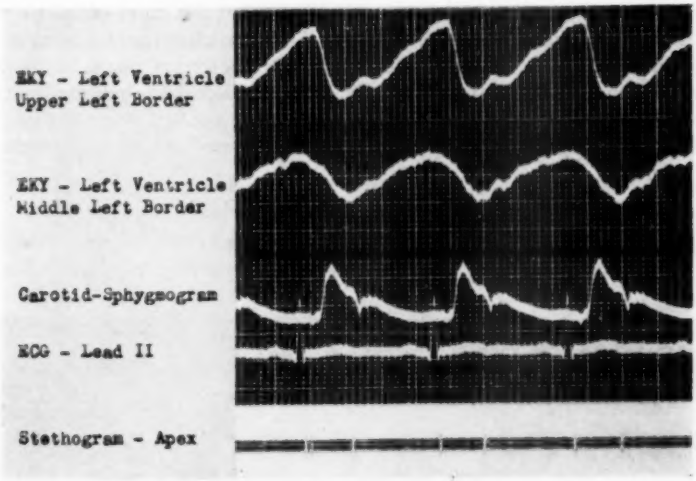

FIG. 10. Samplé of simultaneous recording of multiple events.

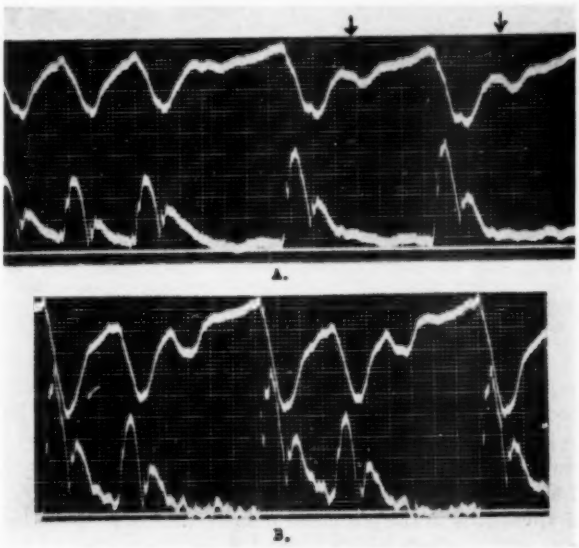

FIG. 11. Ventricular premature contractions.

Noted clinically and on ECG of subject with no other sign of heart disease. A—Lower left ventricle (PA). Normal rhythm changing to bigeminal. Arrow marks premature contraction which bulges, but fails to open semi-lunar valves. B—Period of trigeminal rhythm, same subject.

Another interesting measurement is that from the onset of the ejection limb on an arterial curve to the incisura, i.e. from opening to closing of the semi-lunar valves. This indicates the effective ejection phase of the ventricle (including protodiastole). Partially studied data indicate that the duration of ejection can be different in the right and left ventricles of man, and is often longer on the right. Katz demonstrated this same phenomenon in animals.[23]

Other Electrokymograms

The EKY is being used to obtain records of such events as heart "density" changes, hilar shadow movements, pulmonary vascular flow, etc. For example, by placing the aperture of the instrument over the body of the ventricle, a record is obtained which resembles the volumetric curve of the ventricle. While similar to the ventricular border curve, it tends to show less effect from positional shift of the heart (figure 9). Such a "density" curve reflects changes occurring with variations in the amount of blood within the heart and alterations in the posterior-anterior thickness of the heart muscle. If the heart was a sphere which expanded and contracted uniformly about the center point at which the electrokymograph was focused, the density change could be used to accurately estimate cardiac output. Actually, the heart is of relatively irregular shape and undergoes mass positional shifts,

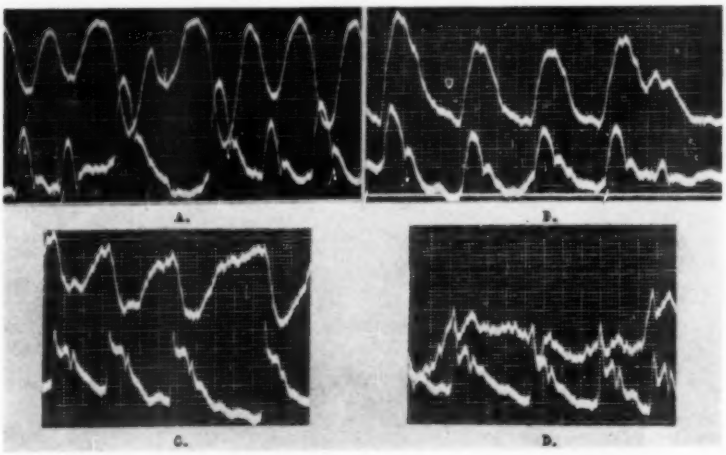

Fig. 12. Auricular fibrillation.

Two subjects with arteriosclerotic and hypertensive heart disease and enlarged hearts. A—Middle left ventricle (LAO—10°). Complexes irregular in rate, rhythm, amplitude and contour. B—Same subject. Pulmonary artery (PA). C—Second subject. Lower left ventricle (PA). Splintering and irregularity of complexes. D—Same subject. Right atrium (PA).

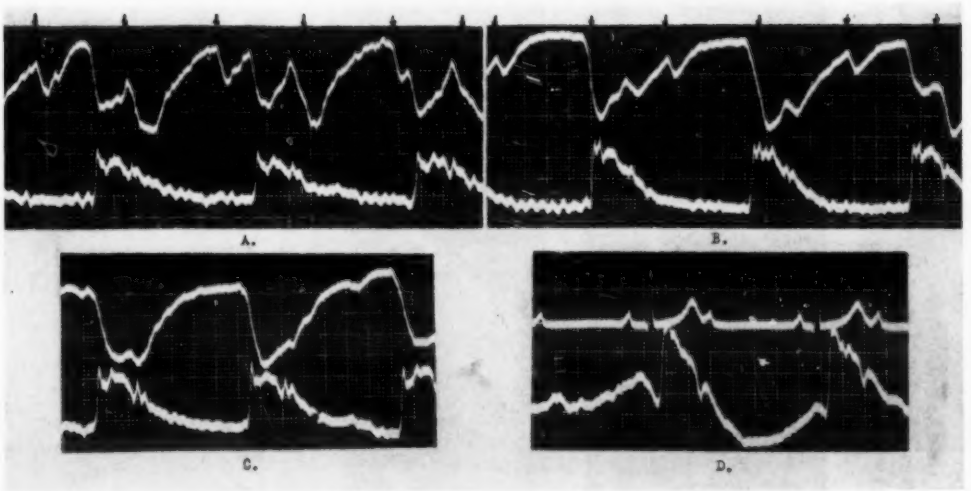

FIG. 13. Complete atrio-ventricular dissociation in subject with calcification annulus fibrosis, etiology unknown. No other signs of cardiovascular disease.

A—Left atrium (RAO). Recurrent descending limbs (arrow) associated with atrial contraction. Effect of ventricular systole evident at about one-half rate of atrium. B—Right atrium (PA). C—Middle left ventricle (PA). Large complexes associated with slow rate and prolonged diastole. D—Electrocardiogram and carotid sphygmogram.

so that the central beam of the x-ray is passing through different thicknesses and areas of heart and blood as the heart moves in its cycle. Nevertheless, investigations are being made with simultaneously recorded ballistocardiogram and EKY to see if some correlation can be shown between these "density" curves and cardiac output.

Mixed-type waves can be recorded from the superior and inferior vena cava. These tracings resemble phlebograms, but superimposed movements

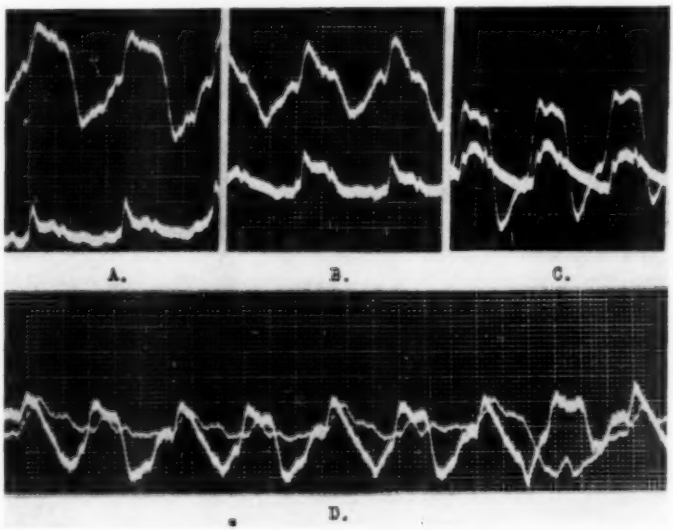

FIG. 14. A and B—Myocardial infarction.

Subject with hypertensive heart disease, enlarged heart and old posterior infarct. Left lower border PA and LAO respectively. Paradoxical motion evident. Outward movement in early systole. Slowly descending plateau as ejection proceeds. Diastolic collapse with inward movement during isometric ventricular relaxation. C—Malignant hypertension with enlarged heart and electrocardiographic evidence of left ventricular hypertrophy. No signs or symptoms of infarction. Paradoxical motion, lower left ventricle (LAO). D—Pulsus alternans in subject with hypertensive and arteriosclerotic heart disease, enlarged heart and old anterior infarction. Middle left ventricle (PA). Note paradoxical movement on all curves with alternating contour of complexes.

of arteries and heart may complicate their interpretation. Arterial type recordings have been obtained from the hilar shadows and the peripheral lung fields (figure 9C). This makes it possible to study pulmonary circulation. The device has also been modified for use as a photo-electric plethysmograph,[10] to record diaphragm movements, and work is in progress to adapt it as a recorder for the ballistocardiograph.

Figure 10 illustrates the simultaneous recording of several events by the special multiple channel instrument to which we have previously referred.

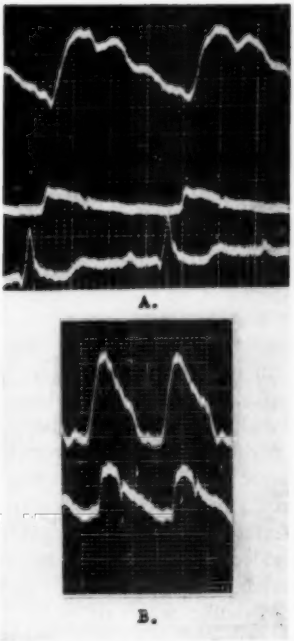

FIG. 15. Bundle-branch block.

Subjects with arteriosclerotic heart disease and classical electrocardiographic evidence of bundle-branch block.

A—Right bundle-branch block. Ejection on pulmonary artery EKY (upper) 0.05 sec. behind that on carotid (middle), i.e. PAc = − 0.05 sec. Lower curve ECG—Lead II. B—Left bundle-branch block. Ejection on pulmonary artery (upper) 0.07 sec. ahead of carotid (lower), i.e. PAc = 0.07 sec. These are significant variations from normal PAc + 0.03 to − 0.01 sec.[17]

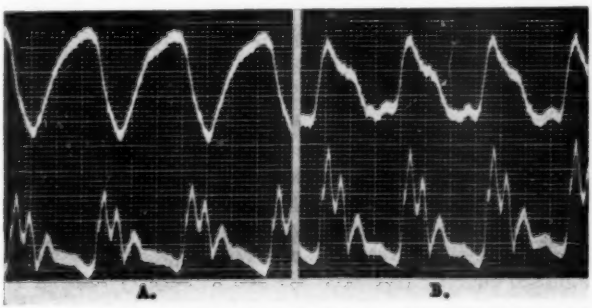

FIG. 16. Aortic regurgitation—subject with luetic aortitis and enlarged left ventricle. A—Middle left ventricle (RAO). Ascending and descending limbs from V-shaped trough with absence of complexes associated with isometric contraction and isometric relaxation on all views. Carotid sphygmogram shows systolic collapse. B—Ascending aorta, note absence of incisura.

The Electrokymogram in Cardiovascular Disease

The primary effort of this group, aside from development of the instrument, has been to study the normal EKY and its variations, especially the ventricular records. A limited number of observations has been made on subjects with cardiovascular disease. A great amount of work must still be done before any attempt to define the "normal" or "pathological" EKY can be made. The following records, figures 11, 12, 13, 14, 15 and 16, are presented, not as pathognomonic EKY patterns, but to demonstrate some of the changes we have noted in the presence of cardiovascular disease and to point out some of the many possible applications of the instrument.

Discussion

The development of the electrokymograph provides an improved method for graphically recording the movements of the borders of the heart and great vessels. Devices used for this purpose in the past have been of limited value because of such factors as difficulties in interpretation and inability to easily record some simultaneous cardio-dynamic event. The instrument has proved a valuable tool in the field of cardiovascular physiology. The simultaneous recording of electrokymograms, sphygmograms, stethograms, etc. should lead to a better understanding of the relationships of movements and pressure changes, of mechanical and electrical events, and to a reëvaluation of many phases of cardiovascular activity.[27, 28]

The value of the instrument in clinical work remains to be defined. Promising results have been obtained in preliminary studies of the arrhythmias and myocardial infarcts such as presented here. It is of interest to note the striking similarity between the ventricular EKY found in some human subjects with myocardial infarcts (figure 14) and the ventricular myogram obtained by Tennant and Wiggers,[29] after they produced experimental infarction in dogs. Both demonstrate clearly "paradoxical" movement of the infarcted ventricular wall. In examinations being done on a large group of older men, we have encountered several instances of paradoxical type movement in subjects with no, or minimal, cardiovascular symptoms and a normal ECG. Records from subjects with valvular heart lesions have been difficult to analyze. It may be as Stumpf [4] said concerning roentgenkymography that the forces involved in the movement of the wall of a chamber in the presence of a valvular lesion are too complicated to permit prediction from theoretical considerations. We have used the instrument to study the movements of aortic aneurysms and mediastinal masses, though no records have been presented. One case diagnosed aneurysm, and another diagnosed tumor, have been verified at surgery and by response to x-ray therapy respectively. As stated before, we have done only a few preliminary studies of cardiovascular disease. It remains to be determined

in what specific types of cardiovascular disease pathognomonic EKY patterns appear and just what clinical value the instrument will have.*

Conclusions

1. The principles of the electrokymograph, the technic of its application and method of interpreting the records have been presented.

2. Electrokymograms from normal subjects and from selected subjects with cardiovascular disease have been demonstrated.

3. The instrument provides a valuable aid for studying the physiology of the cardiovascular system in human subjects and it warrants continuing evaluation of its possible clinical application.

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* Since this paper was submitted, additional papers on the clinical application of electrokymography have been published or have been accepted for publication. References to this material have been added.[30, 31, 32, 33, 34]

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SECONDARY AMYLOIDOSIS IN SPINAL CORD INJURY *

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RECENT reviews of the literature reveal an awakening of interest in the study of amyloidosis.[1, 2, 3, 4, 5] The occurrence of this lardaceous pathological process in relationship to spinal cord injury had not been noted previously, with the exception of a case reported in 1867 by Fagge.[6] A large number of spinal cord injuries, resulting from World War II, are under observation in Veterans Administration hospitals. Sufficient time has now elapsed for these patients to be subjected to the effects of wasting disease, tissue atrophy and repeated infections. Secondary amyloidosis in this group of patients then might be expected to occur.

The purpose of this manuscript is to report four cases of secondary amyloidosis found at autopsy in patients with spinal cord injury and to discuss the clinical significance of this process.

Case 1. This 22 year old white male was injured in a fall November 13, 1942. Following this injury a physiologically complete myelopathy at the level of D–4 was present. His course subsequent to this event was the usual one of decubitus ulcer and recurrent urinary infection with renal vesicular calculi. The patient maintained a poor state of nutrition throughout this time.

On March 28, 1947, he was admitted to this hospital for treatment and care of his spinal cord injury. At this time he was markedly undernourished and had multiple decubitus ulcers. His urinary status was as follows: suprapubic catheter, penoscrotal fistula, bilateral renal calculi and chronic cystitis. The following were the laboratory data: urine albumin 2 plus, no casts or cells in urine; red blood cells 3,400,000; hemoglobin 12 gm.; total protein 6.5 with A/G ratio 1.5. X-ray pyelography revealed nonfunction of left kidney and small multiple calculi in right kidney.

Course in Hospital: A high protein, caloric and vitamin diet was instituted with improvement of ulcers but only slight nutritional response. Gross hematuria developed in July. Slight rectal bleeding occurred in September. Proctoscopic examination on September 10, 1948, revealed edema and injection of the mucosa. The patient suddenly became nauseated and oliguria appeared. Blood pressure at this time was 50 mm. of mercury systolic and 30 mm. diastolic. Red blood cells 3,300,000, hemoglobin 9.2 gm., and non-protein nitrogen 56 mg. per cent. Cystoscopic examination revealed calculi had moved into the right ureter. An emergency right nephrotomy was performed to establish urine flow. There was no improvement in renal function from this procedure. Shock continued. On September 13, 1947, jaundice developed. The icteric index was 33, with no urobilin in feces or urine. On September 16, the non-protein nitrogen was 123 mg. per cent; the urine contained 4 plus albumin; the

* Received for publication March 9, 1948.

From Paraplegia Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tennessee. Published with permission of Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

cephalin flocculation test was 4 plus. Oliguria and azotemia progressed, leading to death on September 20, 1947.

Pathological Findings: Autopsy examination revealed amyloid infiltration in the kidneys, liver, spleen and adrenal cortex (figures 1, 2, 3, 4).

Case 2. A 26 year old white male entered this hospital March 29, 1947, with a history of paralysis for three years. Before admission, a disarticulation of the right femur at the hip joint had been performed for chronic osteomyelitis. Nutritional state was excellent; no decubitus ulcers were present but the patient had a large urinary residual. Gynecomastia was present, however, though liver function tests were normal. On April 21, 1947, bladder neck resection was performed to reduce the urinary residual. Because of spasm of the muscles of left leg and dislocation of left hip, an arthrodesis was done on the left hip joint in June, 1947. Urinary infection occurred in October, with a calculus demonstrated in the right kidney. A right nephrolithotomy was performed October 7, 1947, and the patient did well until October 19, when a phlebothrombosis developed in the left femoral vein with a small infarction of the lower lobe of the left lung. An emergency ligation of the common femoral vein was performed. The patient continued to cough blood and on November 3, 1947, a pneumonic process in the upper lobes was noted, necessitating an oxygen tent. The pneumonia improved with antibiotic therapy. Generalized edema appeared November 5, and his condition was further complicated by a nonspecific diarrhea. The total blood proteins decreased rapidly to 5 gm. Oliguria developed and subsequently the non-protein nitrogen of the blood increased steadily to 135 mg. per cent. The patient became comatose November 9, 1947. He died on November 11, 1947, of uncontrolled kidney failure complicated by pneumonia and ileus.

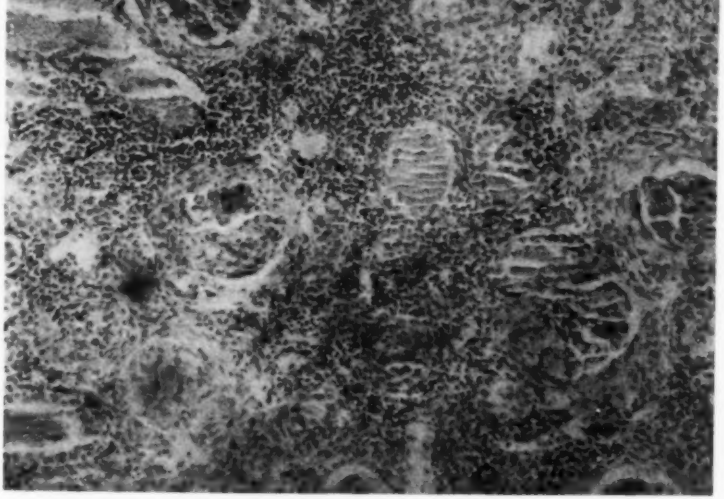

FIG. 1. *Case 1.* Renal interstitial tissue shows round cell infiltration and fibrosis. Glomeruli show varying stages of atrophy and amyloid infiltration. Amyloid degeneration is seen in proximal and convoluted tubules.

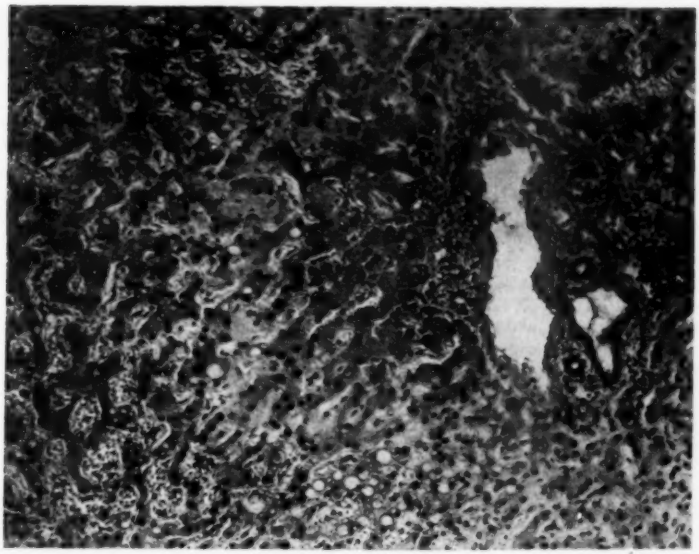

FIG. 2. *Case 1.* Liver. Showing fibrosis and round cell infiltration with pale staining amyloid material replacing the parenchymal cells.

Pathological Findings: Amyloid deposits in the spleen and kidneys were found at autopsy (figures 5 and 6). There was a bronchopneumonia and pulmonary infarct (left). A gastric and duodenal ulcer were also noted.

Case 3. In April, 1945, a 25 year old male received a gunshot wound, fracturing the fourth thoracic vertebra. A complete transverse myelopathy followed this injury. Laminectomy and suprapubic cystotomy were performed three weeks after injury. Decubitus ulcers of the ischium and trochanteric areas developed early. The ischial decubitus ulcers were closed surgically, but the ulcers in the trochanteric region at no time healed. Before admission to this hospital there was no history of renal infection or of renal calculi.

He was admitted to this hospital on January 16, 1948, as a transfer from another hospital. There were large decubitus ulcers over both trochanters, the right thigh and the sacrum. One month before admission, he suffered third degree burns of both feet. These extremities became infected following the burn, and bilateral edema was present on admission. During December, 1947, while still out of the hospital, the patient developed several loose stools which were controlled with paregoric and bismuth. Several days before his admission to this hospital he developed severe diarrhea, that was uncontrolled by previous measures. Laboratory data were negative, except for a mild hypochromic anemia and low serum protein (5 grams with A/G ratio of 1 to 1). X-ray study of kidneys, ureter, and bladder revealed no calculi.

Course in Hospital: Patient was placed on a low residue diet and given sulfaguanidine and paregoric to relieve diarrhea. Bacteriological examination of stools was negative throughout the illness. On January 19, 1948, three days after admission a 3 plus albumin was present in the urine. This albuminuria continued, varying between one and three plus. The severity of the diarrhea fluctuated, but was never

completely controlled. A sigmoidoscopic examination revealed a congested mucosa with petechial hemorrhages. The total serum protein had dropped to 4.3 grams by February 5. The cephalin flocculation test at the same time was 4 plus in 48 hours. Due to the similarity of these events with those of the cases presented above, the diagnosis of amyloidosis was suspected. Congo red test was performed but was negative. Attempts to improve nutrition by use of intravenous protein hydrolysate failed to elevate the serum protein or improve nutrition. Nausea, headache and oliguria appeared suddenly on March 10, 1948. Associated with this was a persistent hypotension of 80 mm. Hg systolic and 40 mm. diastolic. This was unaffected by adrenal cortical extract. Blood chemistries of March 8, 1948, showed non-protein nitrogen 40 mg. per cent, total protein 3.6 gm. with A/G ratio of .6 to 1. The non-protein nitrogen increased within a week to 132 mg. per cent and the CO_2 combining power decreased to 30 per cent. Hypotension increased until shock level of 30/20 was reached on March 8, 1948. Respirations became labored. Cyanosis developed and death occurred on this date.

Pathological Findings: The spleen, kidneys, liver and adrenals were enlarged. Amyloid deposits were noted in all of these organs, replacing most of the normal tissue.

Case 4. This 27 year old white male had been wounded in the chest on September 9, 1944 by a shell fragment, with accompanying fracture of the twelfth thoracic vertebra. There was immediate and complete loss of motor function and sensation below this level. A laminectomy was performed immediately and the patient transferred to the Zone of the Interior. While he was still in the Army a cordotomy was done to relieve pain. Several decubitus ulcers developed, but healed without injury. A right nephrolithotomy was performed March 12, 1946, but it was necessary to leave a large calculus. When the patient was transferred to the Veterans Administration

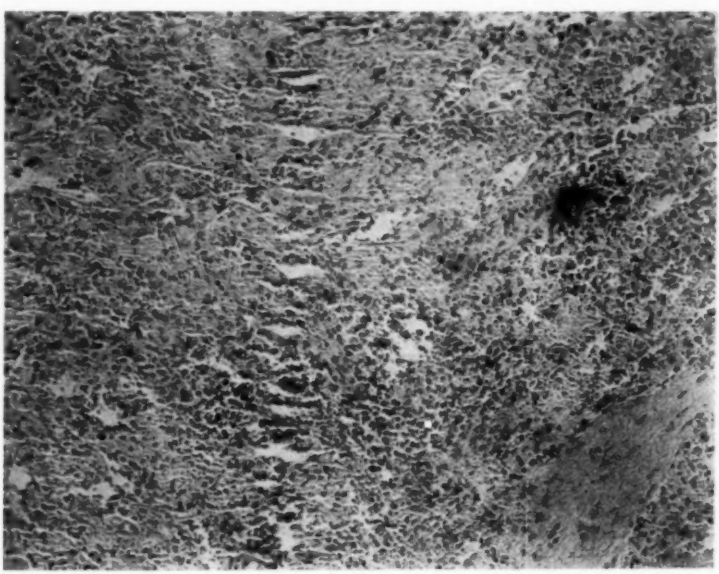

FIG. 3. *Case 1.* Spleen. No definite architecture is present. Stroma and malpighian corpuscles are replaced by acellular, pale staining amyloid material.

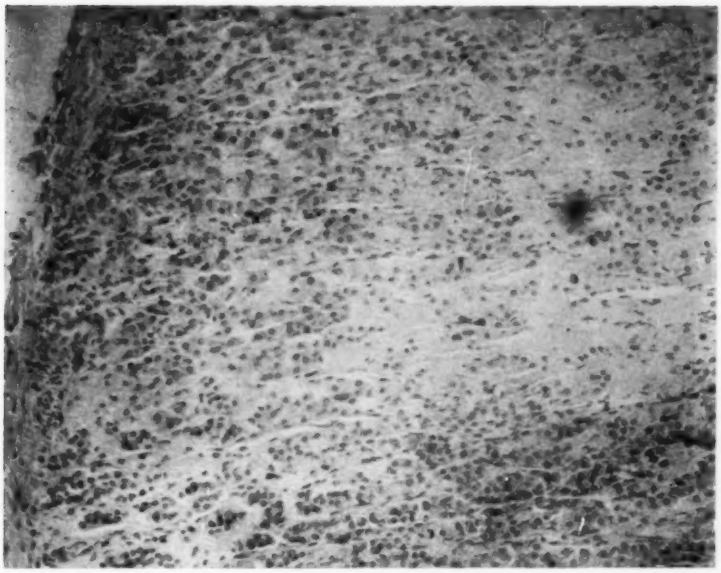

FIG. 4. *Case 1.* Adrenal cortical tissue almost completely infiltrated with amorphous, pink staining amyloid material.

on June 6, 1946, a decubitus ulcer of the right hip, a stag-horn calculus in the right kidney, and osteomyelitis of L–1 and L–2 vertebrae was present. In September 1946, the patient developed infectious hepatitis. Calculi developed in the right kidney and were removed November 8, 1946. A transurethral vesical resection was performed in March, 1947, with improvement of renal function. Several episodes of urinary infection occurred and calculi developed in both kidneys. Patient left the hospital against medical advice for six months. On September 6, 1947, he was admitted with the previous diagnoses, plus a draining sinus in the suprapubic ulcer and multiple rat bites of the lower extremities. His course following readmission steadily declined. The bilateral stag-horn calculi increased in size but the patient's general condition was too poor to consider further surgical intervention. There were repeated episodes of urinary infection and one plus to three plus albumin was always present. Liver function testing on January 15 showed bromsulfalein 20 per cent, cephalin flocculation 3 plus in 48 hours, total protein 6.5 grams and A/G ratio 1.2 to 1.

In January, 1948, amyloidosis was suspected but Congo red test was negative. Examination of the gingival tissue showed no evidence of amyloidosis. On February 3, 1948, suprapubic cystotomy was performed to increase renal function. On February 27, 1948, a spontaneous femoral thrombophlebitis, left, occurred and a bilateral femoral vein ligation was performed. The patient lost strength rapidly. Transient edema of face, genitalia and abdomen was observed the latter part of March. Total proteins at that time were 4.7 grams with .6 to 1 A/G ratio. Severe, uncontrollable diarrhea developed about one month later. Non-protein nitrogen gradually rose to 74 mg. per cent on April 4, 1948. One week before death the urine became grossly bloody. Oliguria developed and was accompanied by clinical evidence of azotemia.

FIG. 5. *Case 2.* Splenic lymphoid stroma is infiltrated with acellular, amorphous, pink staining material, characteristic of amyloidosis.

FIG. 6. *Case 2.* Renal glomeruli demonstrate marked atrophy and infiltration with amyloid material. Profuse tubular degeneration is present and it contains the pink staining material.

On May 12, 1948, respirations became labored and shallow. Constant projectile vomiting and Cheyne-Stokes respiration developed, followed by death.

Pathological Findings: At autopsy, amyloid deposits were noted in the kidneys and adrenal cortex. There was also periportal hepatic cirrhosis and ulcerative colitis.

Discussion

Spinal cord injury is accompanied by a triad of inflammatory processes: decubitus ulcers, chronic osteomyelitis and urinary infections. In addition to this triad there is a profound disturbance of metabolism that has not been elucidated. The fact that these patients now live long enough to be encumbered by the above processes makes amyloid degeneration a distinct possibility.

The clinical findings of secondary amyloidosis vary with the organ involved and the amount of amyloid deposited. The primary disease often masks the findings.[7, 8, 9] If the liver and spleen are involved, these organs usually will be palpable. Abdominal distention may accompany these findings. Purpura has been reported in several cases with splenic amyloidosis.[10] Jaundice, seen in Case 1, is extremely rare, having occurred only four times in the previous literature.[11, 12] Albuminuria obviously is a consistent sign when amyloid degeneration involves renal tissue. If albuminuria is excessive, hypoproteinemia will result. The edema of hypoproteinemia appears late in the course of the disease. Hyaline and granular casts may also appear. There is loss of the power of concentration of the kidney due to tubular damage. The severe azotemia that preceded coma and death in the cases presented is an unusual finding in amyloid disease.[7] When renal insufficiency and uremia occur, the process is irreversible and death is rapid as is illustrated by these cases. Adrenal involvement is a common finding.[10] Addison's disease as a result of amyloid deposits in the adrenal is rare; however, three of these cases presented the clinical picture of subacute adrenal cortical insufficiency.

The clinical diagnosis of amyloidosis in spinal cord injury is difficult because the findings described above are present in the ordinary complications of this injury. Malnutrition and metabolic disorders occur soon after spinal shock. Hepatomegaly is seen frequently. It has been noted in 33 of 250 patients on the Paraplegia Service here. The cause of this enlargement of the liver has not been elucidated. Cases 1 and 3 are the only patients of the 33 mentioned above in which this hepatomegaly proved to be associated with deposits of amyloid in the liver. Albuminuria is also a frequent finding resulting from urinary infection and calculi in the bladder and kidney accompanying spinal cord injury.

It is interesting to attempt to explain the cause of the non-specific bloody diarrhea in the cases presented. Two peptic ulcers were present at necropsy (Cases 2 and 4), one gastric and the other duodenal. In Case 2 there was some evidence of bleeding from the gastric ulcer. Case 4 presented ulcerative colitis. There were no amyloid deposits in the gastrointestinal tract in

any case. The mucosa of the large bowel of all cases showed congestion and hyperemia. These pathologic findings suggest that the diarrhea may have been connected with the uremic state present in these patients.

Amyloidosis associated with spinal cord injury is an unusual but not an unexpected occurrence. Since the introduction of chemotherapeutic and antibiotic agents and surgical procedures a certain measure of success has been accomplished in the treatment of the infectious complications of spinal cord injuries. This elimination of infection can be a factor in the prevention of amyloidosis. The use of whole liver as advocated by Grayzel and Jacobi [13] may help in the treatment of this irreversibly destructive pathological process. These combined factors should improve the prognosis of amyloid disease complicating spinal cord injury.

SUMMARY

1. Four cases of amyloidosis proved at autopsy occurring in spinal cord injury are presented.

2. The clinical course of the patients is that of secondary amyloidosis associated with renal involvement.

3. The expected incidence of this process in spinal cord injury is illustrated by this report.

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THE DIAGNOSIS OF PNEUMONIA PRECEDING TUBERCULOSIS *

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A LARGE proportion of the patients admitted to the Tuberculosis Division of the Baltimore City Hospitals for the first time had previously been acutely ill with what was diagnosed as pneumonia. The acute illness occurred at a period when it might be assumed that a tuberculous process was present. In most instances the disease was in a far advanced stage when the diagnosis of tuberculosis was made subsequent to the acute illness. In some cases, death occurred from tuberculosis soon after acute symptoms suggesting pneumonia, and diagnosed as such, developed. Many more individuals gave histories of influenza and grippe a relatively short time before the diagnosis of tuberculous infection was established.

An attempt has been made to analyze those cases of tuberculosis with acute symptoms, excluding those called influenza and grippe, and including only those with the most severe picture namely those which a physician had called pneumonia. Five hundred charts were selected at random from the files of the City Hospitals Tuberculosis Division and the records of those patients with a history of pneumonia selected for further study. When the patient had been treated at home by a private physician, the history as given by the patient had to be relied on completely. When patients had been hospitalized and the diagnosis of pneumonia made, either the old chart or an abstract of the record was obtained, if possible.

It was found that of the 500 patients, 71 or 14.2 per cent gave a history of pneumonia with a time relationship such that it was possible or likely that the illness was related to the tuberculous infection in some way. Many more gave a history of an acute illness called influenza, but these were not investigated further. Of the 71 patients, 48 had been treated for pneumonia at home and 23 had been cared for in a hospital. The age, sex, and racial distribution were similar to those of the Tuberculosis Division except for the small number of Negro women in the group, nine in all. This estimate of the proportion of patients with tuberculosis, who had been diagnosed as pneumonia, does not include those instances in which the symptoms of the acute illness or the clinical course of the disease had suggested tuberculosis and in which further studies had then established the diagnosis of that disease during the hospital stay. Thus, in almost 15 per cent, it was judged that some harm had been done by diagnostic failure either to the patient or his contacts.

There are three explanations of why pneumonia had been diagnosed: (1)

* Received for publication December 13, 1947.
From the Division of Tuberculosis, Baltimore City Hospitals.

TABLE I

Showing Clinical Data on Patients Discharged from General Hospital with Pneumonia Preceding Tuberculosis
(Only those included, on whom adequate information available)

Name	Sex	Age	X-Ray Reading Gen. Hospital	WBC— Gen. Hosp.	Temperature	Elapsed Interval	X-Ray TBC Hosp.
1. H. W.	WF	39	Mottled fibrous densities in left first interspace. Densities in lower left chest and hilum. No essential changes, later. Considered atypical pneumonia.	8,400	104°(R) on admission. On penicillin and sulfadiazine, drop to normal in five days but persistent low grade fever to 99.6° on discharge.	11 mos.	Diffuse infiltration involving entire left lung, also infiltration at right base. Positive sputum.
2. E. B.	CM	47	Mottled shadows, density over entire left lung and lower portion of right. Marked clearing hilar region later.	18,800–12,000 11,000–14,000	104 to 105° on admission—gradually subsiding but never disappearing completely. No chemotherapy.	5 mos.	Right lung clear. On left—infiltration from apex to fourth rib with mottling to base.
3. J. H.	CM	47	Large area of consolidation base of right lung with fibroid infiltration left apex. Discharged, diagnosis—acute lobar pneumonia RLL type undetermined with delayed resolution.	32,400	Temperature fell by crisis. No chemotherapy.	Approx. 3 yrs.	1st admission for TBC, x-ray reading not available.
4. J. M.	CM	48	Consolidation right upper lobe.	2,500–17,400	104 to 101° to low grade fever after one week. Sulfonamides.	3 mos.	Infiltration right upper lobe.
5. J. F.	WM	71	Pneumonic density, left upper lobe.	8,200–9,000	100–104° for nine days, went down to 99.4°.	2 mos.	Bilateral apical disease minimal.
6. E. R.	WM	50	Consolidation upper ¾ right lung, no change until two months later when slight clearing was reported.	5–8,000	From 105° to normal in five days. Low grade thereafter.	1 year	Far advanced disease right upper lobe with cavity.

TABLE I—*Continued*

Name	Sex	Age	X-Ray Reading Gen. Hospital	WBC— Gen. Hosp.	Temperature	Elapsed Interval	X-Ray TBC Hosp.
7. J. C.	CM	23	Minimal infiltration infraclavicular area. Râles heard over LLL considered to be site of pneumonia.	5–11,000	105° on admission. Rapid fall to 99° with sulfonamide.	5 years	Far advanced bilateral.
8. J. K.	WM	57	Clouding in left mid-lung, patchy infiltration in left base and old fibrous infiltration in right upper lung.	18,600	Temperature persisted. Empyema blamed. Positive blood culture for pneumococcus not typed.	1 year	Location—upper ⅔ both lungs, positive sputum. Died in 13 days.
9. T. R.	CM	43	Dense clouding through greater portion of upper right lung.	24,500	Down to normal in one day; after seven days up to 99 to 100°. Recurrence. Temperature again to normal. Received sulfonamides.	9 months for diagnosis.	Right upper lobe moderately advanced.
10. G. M.	WM	55	Consolidation LUL, some clearing on serial films.	16,500 with 89% polys.	Nineteen days for temperature to return to normal.	2½ years	Left upper lobe.
11. A. B.	WM	55	Patches of bronchopneumonia. Each lower lung.	7,300	100 to 102° for eight days; then 99 to 100° subsiding in one week.	38 mos.	Consolidation upper half left, patchy right mid-lung.
12. S. M.	CF	30	Infiltration left and right apex and right base probably due to resolving pneumonia. No change before discharge.	28,850	103° on admission to normal in three days. Secondary elevation. Received sulfonamides.	15 mos.	Throughout both lungs bilaterally.
13. T. M.	WM	65	Density over entire left lung field which showed some clearing.	19,000 down to 10,500	100 to 101°, gradually fell to 99 to 100° on discharge with penicillin.	7 mos.	Bilateral extensive.

The patient had pneumonia without tuberculosis. The illness may or may not have contributed to the later development of tuberculosis. (2) There was a pneumonia superimposed on a tuberculous infection. (3) The findings were misinterpreted as being due to pneumonia when actually due to tuberculosis. It is probable that the largest number of cases fall in the last group, of which the following case histories are illustrative:

A 38 year old white man was admitted with tuberculosis on June 27, 1945. He had complained of malaise and fatigability for two years but of no other significant symptoms. In the late winter of 1944, he developed a cold with a fever and cough.

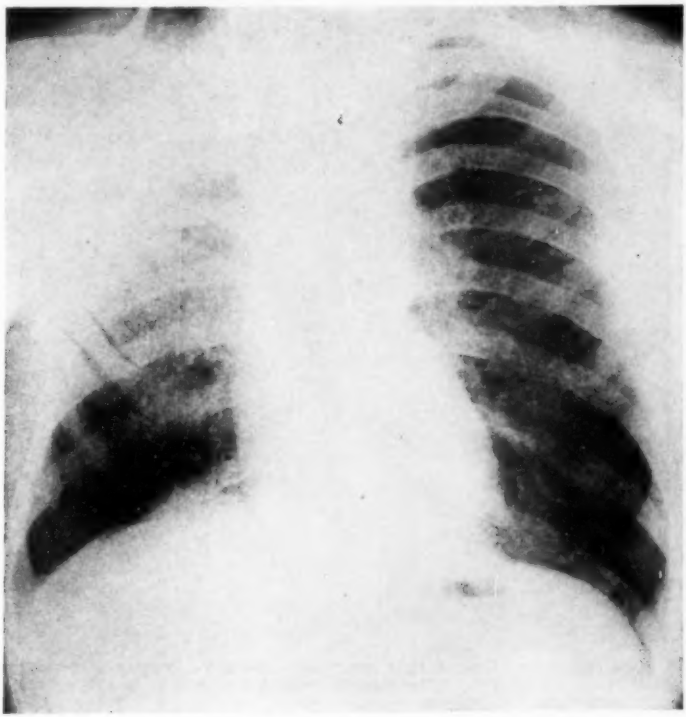

FIG. 1a. Consolidation right upper lobe. Diagnosis: pneumonia.

This was diagnosed as bronchopneumonia and after treatment with sulfonamide and bed rest at home, he felt fairly well. In March 1945, there was another acute episode and again the symptoms subsided on rest and chemotherapy. In May 1945, the symptoms recurred. A roentgenogram showed far advanced tuberculosis.

A 50 year old white man was first admitted to Baltimore City Hospital on March 18, 1942. His temperature was 105° F. and a roentgenogram showed consolidation of the upper two-thirds of the right lung. His temperature subsided within five days

while he was on sulfonamide therapy. The leukocyte count ranged between 5,000 and 8,000. One month after admission, there was only slight clearing of the consolidated area. Sputum studies yielded a type 5 pneumococcus. One year later he was admitted with a positive sputum and a diseased right upper lobe.

A 48 year old Negro male was admitted to a general hospital in November of 1943. On admission there was consolidation of the right upper lobe. The temperature was 104° and fell to 101° within a week. The leukocyte count was 2,500 on admission but rose to 17,400 after four days. Type 12 pneumococcus was obtained from the sputum by mouse inoculation. The discharge diagnosis was unresolved pneumonia. In May of 1944, he was admitted to City Hospitals with positive sputum and disease of the right upper lobe.

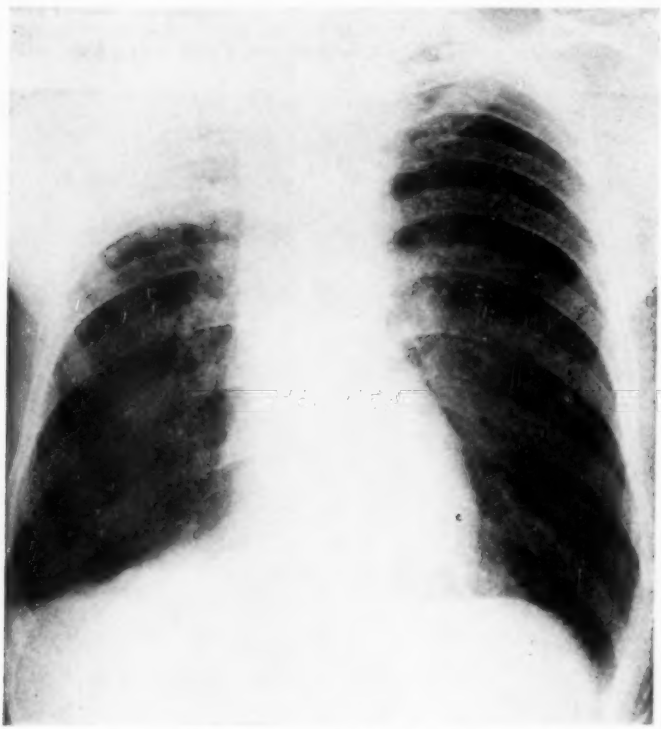

FIG. 1*b*. One year later. Disease right upper lobe. No acute symptoms, sputum positive for tubercle bacillae.

Several instances were encountered where non-tuberculous pneumonia had in all probability accompanied a pulmonary tuberculosis:

A 29 year old Negro male was admitted to a general hospital in September of 1942 with the complaint of severe pain in the left chest of 12 hours' duration. The

temperature was 100° rectally with a leukocyte count of 20,400. Physical and roentgenologic signs indicated lobar infiltration at the right base. In spite of physical signs at the right apex there was no roentgenologic evidence of disease in that area. No pneumococci were found in the sputum but on two occasions acid fast organisms were found. He was transferred to the City Hospitals, where the positive sputum was confirmed. The consolidation at the right base cleared; a minimal degree of infiltration at the right apex remained. He signed out after a few months of hospital care. In 1946, he was re-admitted in a critical condition with far advanced disease.

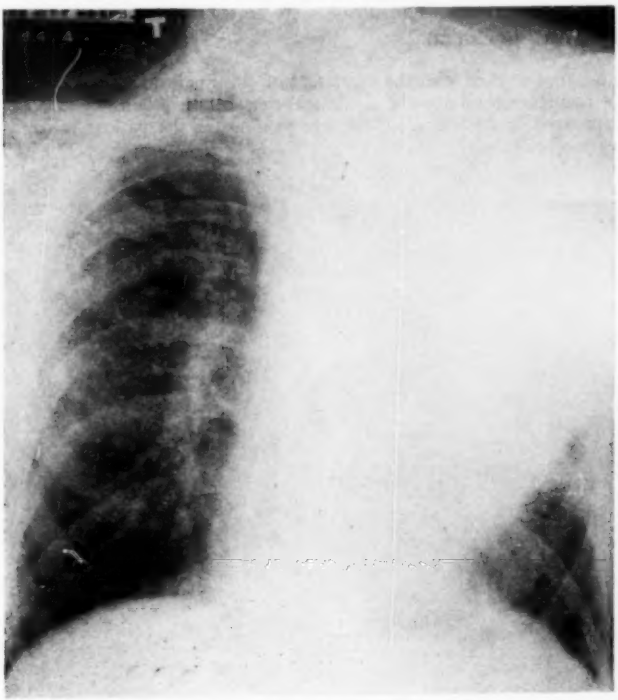

FIG. 2a. Acute onset of illness, consolidation of left upper lobe. Five weeks later: some resolution of process. Sputum negative for acid fast organisms.

A white man of 55 was first admitted to the City Hospitals in March of 1944. The temperature was 103°, the leukocyte count 16,500 with 89 per cent polymorphonuclears. The roentgenogram showed consolidation of the left upper lobe. The temperature returned to normal slowly while the patient was under treatment with sulfadiazine. Five sputum examinations were negative for acid fast organisms. No pneumococci were detected. In October 1946, he was admitted again with an almost identical story. The temperature was 105° and the white count 23,000. He was severely dyspneic. The temperature and white count returned to normal after 24 hours as did his respiration, during the administration of penicillin. The sputa were

positive for tuberculosis. The roentgen-ray of the chest was virtually identical with that obtained in 1944. It showed dense infiltration in the left upper lobe and perihilar density on the right which rapidly cleared.

There are a number of factors which account for the difficulty in distinguishing clinically between acute non-tuberculous pneumonia and pulmonary tuberculosis:

(*a*) The first definite clinical symptoms of tuberculosis may consist of an episode of high fever which subsides in a few days. Such cases are not always advanced in extent.

In a hospital worker with the complaint of chest pain and sudden onset of fever of 102°, a roentgenogram showed a minimal tuberculous lesion. The symptoms and fever disappeared in 24 hours. Now, five years later the patient has far-advanced pulmonary tuberculosis.

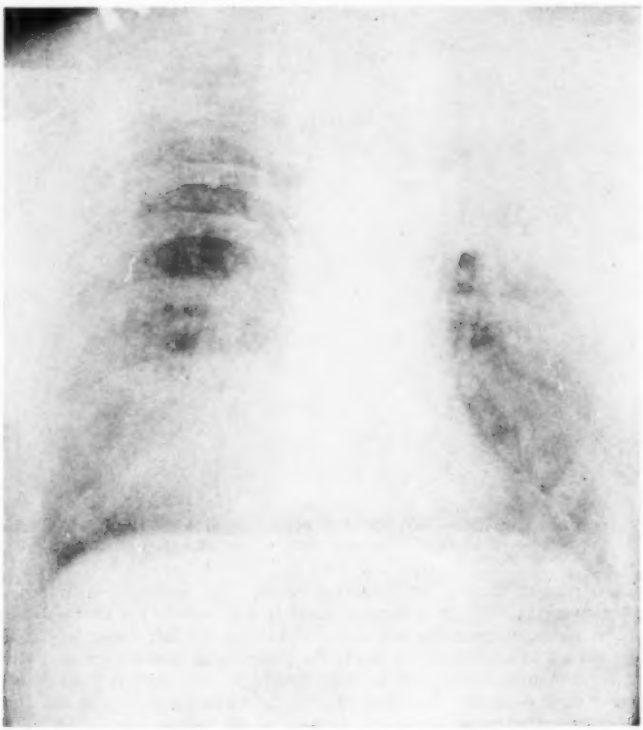

FIG. 2*b*. Readmission film 19 months later. Fever, dyspnea responding promptly to penicillin, positive sputum. Infiltration above right diaphragm completely resolved.

(*b*) The white count may be elevated in tuberculosis to as high levels as in lobar pneumonia.[2] It has been stated that one-fourth of the patients with far-advanced disease have white counts between 12,000 and 18,000, on admission.

(*c*) The fact that the tuberculous process may be restricted to a lower lobe may suggest a non-tuberculous pneumonia.[3]

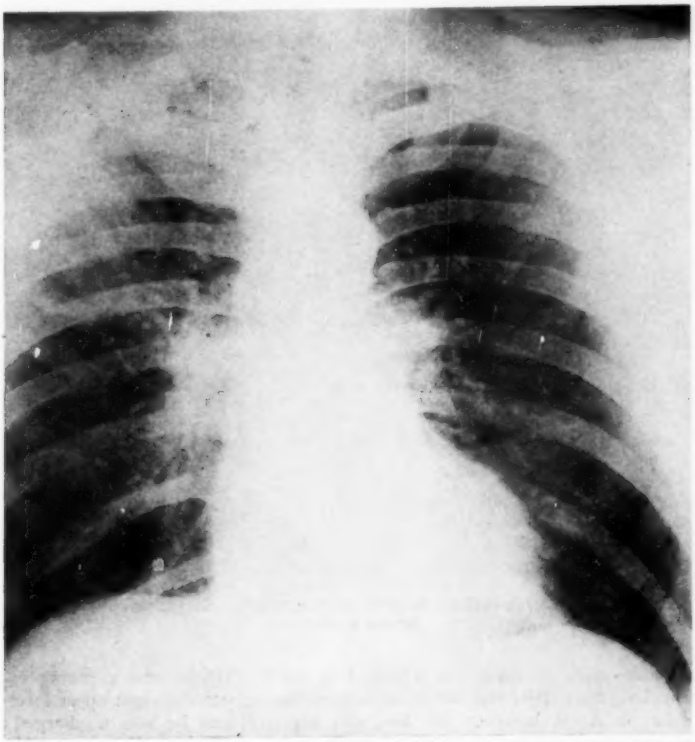

FIG. 3*a*. Film taken on outpatient basis. No acute symptoms, no sputum obtained. Diagnosis of tuberculosis made because of film.

(*d*) In early tuberculosis prior to caseation there may be great difficulty in obtaining a positive sputum.

(*e*) Even the course of the disease, which is usually decisive, may at times prove misleading. While in general non-tuberculous pneumonias resolve in a few weeks and tuberculous infiltrations persist, there are exceptions to both of these rules. Primary atypical pneumonia has been known to give roentgenographic changes for three months.[6] On the other hand, exudative, tuberculous lesions may disappear within the same length of time.

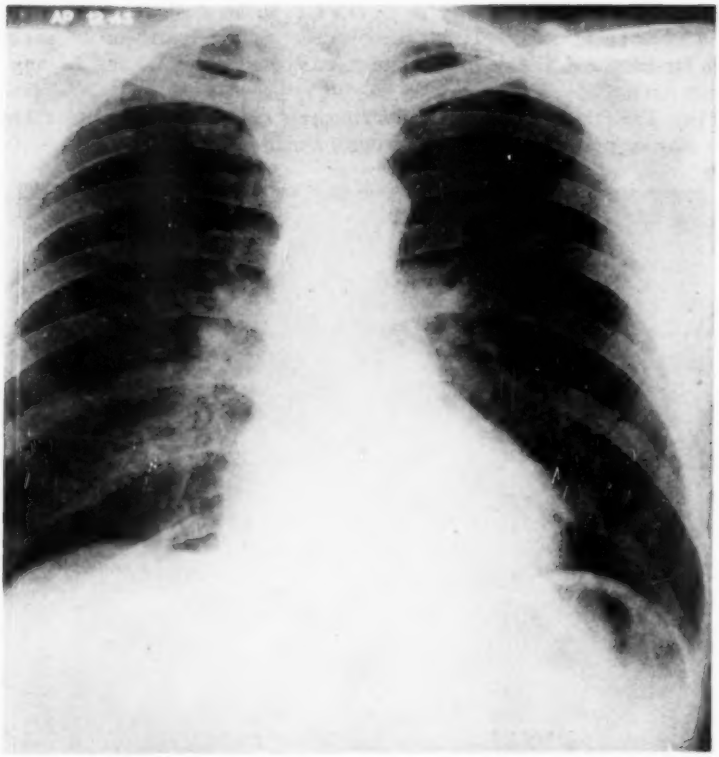

FIG. 3*b*. Admission to tuberculosis hospital in four months. Negative chest, discharged to mental institution.

A white male alcoholic was admitted in April, 1943 because a roentgenogram taken in December, 1942 had shown infiltration throughout the right upper lobe. On admission in April, however, his film was negative, and he was discharged to a mental institution because of delirium tremens a few days after admission. One year later he was readmitted with a far-advanced tuberculous process throughout both lungs and a positive sputum.

In this case unequivocal proof that the original lesion was tuberculous is, of course, lacking, but there have been reported instances similar to this where the initial diagnosis of tuberculosis was more positive. Ornstein, Ulmar and Dittler [5] have described a picture of benign, exudative tuberculosis where the exudative lesion disappears entirely. They collected 58 cases, most of them with positive sputum, in whom all roentgenographic evidence of tuberculosis cleared within six weeks to several months. Amberson [4] in

discussing the process of resolution states that it proceeds slowly and stops at the barriers of unresolvable, caseous centers. It is certainly conceivable that, if there is minimal caseation, resolution may be complete enough so that the residual caseous center may be invisible on the roentgenogram.

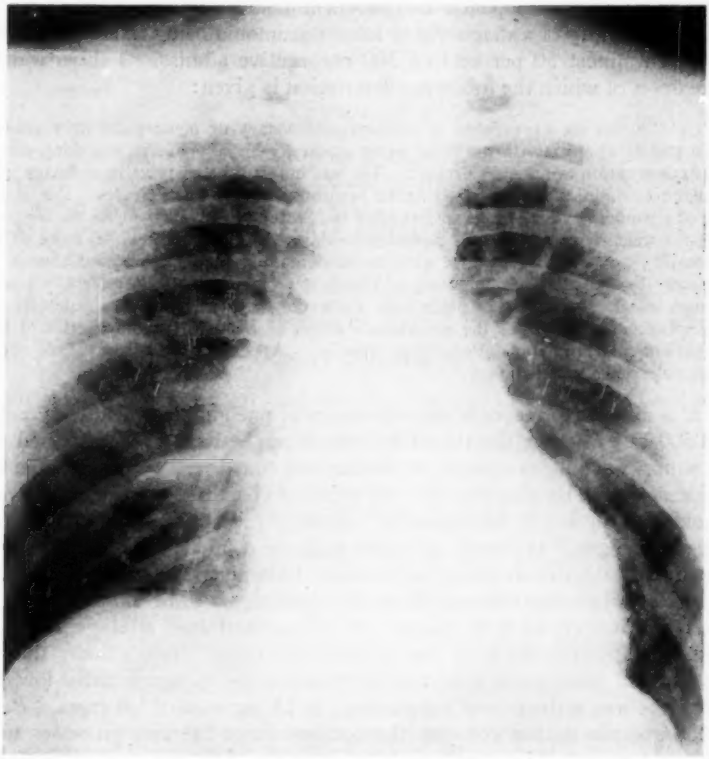

FIG. 3*c*. Readmission to tuberculosis division 15 months later. Positive sputum.

In view of these facts, it is not difficult to understand why difficulties in diagnosis may arise as between a non-tuberculous pneumonia and pulmonary tuberculosis.

DISCUSSION

Very little is found in our literature concerning an antecedent history of pneumonia in tuberculosis. Flick [7] is quoted as stating that one-fifth of all tuberculous patients gave previous histories of pneumonia. Baum and Amberson [8] consider the possibility that these and other reported instances

of patients with pneumonia prior to tuberculosis were initially, in fact, tuberculous. An acute onset of tuberculosis, according to Pinner [9] occurs in about one-half the cases. Farber and Clarke [10] have reported 100 cases admitted to a general hospital for non-tuberculous causes, who were found to be tuberculous. None of these cases was admitted with the diagnosis of pneumonia. In an emphatic and eloquent address, Rist [11] pointed to the strong possibility of a diagnosis of lobar pneumonia being made in tuberculosis. In almost 50 per cent of 300 consecutive admissions there was an acute onset of which the following description is given:

> . . . "it has the appearance of an acute pulmonary or pleuropulmonary episode. Chills and fever initiate it, the fever being generally high. Pain in the sides, coughing, expectoration are always present. The sputum may be rusty as in ordinary lobar pneumonia; dullness or flatness, tubular breathing, and crepitant râles. But it is a kind of pneumonia which either aborts after two, three or four days or on the contrary, drags on much longer than the classical nine days, becoming meanwhile, more or less atypical". . . . "The first stage with its sudden onset may be followed almost immediately by the classical symptoms of manifest pthisis. But it is generally not so. In most instances what takes place after the acute onset is a phase of quiescence or semi quiescence which has the unfortunate effect of appeasing the anxieties of both the patient and physician. Fever has subsided. Appetite comes back. One speaks of convalescence and recovery."

It is difficult to reconcile the occurrence of pneumonia in 14.2 per cent of our 500 cases during the time tuberculosis might have been suspected and the almost unanimous opinion of the unusual concurrence of pneumonia and tuberculosis. The idea that the two together constitute a rarity is so widespread that an article has appeared relatively recently describing two such cases.[12] Hogan [13] reviewed 111 cases with the combined diagnosis of pneumonia and tuberculosis occurring between 1936 and 1944 and found the incidence of tuberculosis among those with pneumonia to be 1.6 per cent. Of the 111, however, 43 were pneumonias of undetermined etiology and more than 50 per cent of the total ran an atypical course. He concludes that the incidence of pneumonia complicating tuberculosis is significantly low and that there was activation of tuberculosis in 15 per cent of his cases. Baum and Amberson do not consider the coexistence of the two processes to be quite as rare as had been supposed. Activation of the tuberculosis was seen to occur when there was an associated suppurative process in the region of the tuberculous disease.

It thus appears that the number of our tuberculous patients giving a history of pneumonia is far greater than would be anticipated from information in the literature. This may be due to our getting the history from the charts of patients in a tuberculosis hospital rather than relying on the discharge diagnosis from a general hospital, as well as the inclusion of the large group of patients who were treated at home for pneumonia. There is evidence that a significant proportion of our 71 patients had an acute tuberculous onset rather than pneumonia. If such mistakes in diagnosis were made in a hos-

pital, it is evident that the possibility of this costly mistake in diagnosis is increased when the patient is treated at home. In recent years with the advent of chemotherapy, and antibiotics, home treatment of acute respiratory disease is more common. There is a tendency to class resistant cases as primary atypical pneumonia. It cannot be too strongly emphasized that the possibility of tuberculosis as the etiologic factor should be kept in mind in all acute pulmonary disease. Sputum examinations and follow-up chest films are of great importance if error is to be avoided.

Summary

Of 500 unselected cases of tuberculosis, 14.2 per cent gave a history of acute illness diagnosed as pneumonia within the period in which tuberculosis might have been expected to be present. This incidence is far greater than would be expected from the reported coincidence of pneumonia and tuberculosis. The findings in an acute tuberculosis may simulate those of pneumonia. There is evidence that in certain of these tuberculous patients, the symptoms resulting in a diagnosis of pneumonia were, in fact, due to tuberculosis.

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CLINICAL OBSERVATIONS ON ATYPICAL LICHEN PLANUS AND RELATED DERMATOSES PRESUMABLY DUE TO ATABRINE TOXICITY *

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Atypical lichen planus is a new clinical entity borne of the tropical phase of World War II. One of the notable events in the military medical history of the Southwest Pacific was the widespread disability of troops because of dermatological disease. Most of the dermatological casualties consisted of those suffering from what was ultimately called atypical lichen planus, from eczematoid dermatitis and from a severe form of exfoliative dermatitis. During the course of the New Guinea campaign, medical officers became aware of a disease of rapidly increasing incidence which bore a striking, though superficial, resemblance to lichen planus, but which was occurring so widely and was so progressive in nature that it soon became obvious that this disease was a new clinical entity. Schmitt and Nisbet are reported [1] to be the first to have called attention to the disease and to have suggested its probable etiology. For want of a better name, and because of its striking similarity to temperate climate lichen planus, it was referred to as atypical lichen planus and by this name it soon became officially identified in the medical nomenclature of the service. As more was learned about this disease it was felt by some that the choice of the name was an unfortunate one, because the disease itself is distinct from the ordinary lichen planus, and because there was much to suggest that it was merely a cutaneous manifestation of a generalized morbid state. Furthermore, unlike lichen planus, there was much to suggest the true etiology of this disease.

In addition to atypical lichen planus two other important dermatological conditions were of related interest. One of these was a bizarre eczematoid dermatitis usually severely exudative. This eruption featured a marked bilateral symmetry almost mirror-like in character. Finally, there were many patients suffering from exfoliative dermatitis wherein no apparent etiology could be demonstrated. This type of exfoliative dermatitis occurred frequently. It was severe; it presented secondary weeping, crusting, and infection, and was sometimes fatal.

We observed patients with atypical lichen planus who had the eczematoid dermatitis associated with it. Patients with atypical lichen planus not infrequently progressed into a state of universal exfoliative dermatitis. On the other hand, many patients with either the exfoliative dermatitis or the less severe symmetrical eczematoid dermatitis often, while under observation, developed lesions which we regarded as characteristic of atypical lichen planus. We felt that it was necessary to identify this characteristic lesion

* Received for publication March 18, 1948.

before a diagnosis of atypical lichen planus could be made. During 1944 and early in 1945, many who were interested in the clinical study of these diseases felt that enough clinical evidence existed to ascribe a common etiological denominator to all three of these conditions.

Clinical Manifestations

Age: In one of our series of 21 unselected cases of atypical lichen planus in enlisted men who were being observed at one time in a ward of an Army General Hospital in New Guinea, the range of ages was from 24 to 46. The average age for the group was 31. This was older than the average age of the enlisted personnel suffering from other diseases in the hospital. The early impression that the disease was more common and more severe in the older age group seemed to be consistently borne out as greater experience with this disease was had.

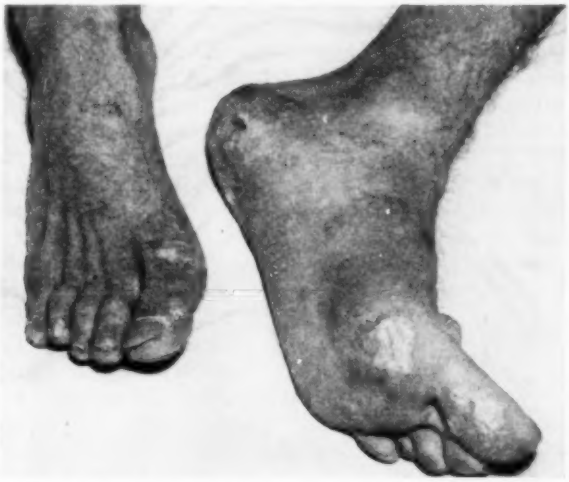

Fig. 1. Case A. B., showing extremely hypertrophic lesions.

Time of Onset: In the same group of 21 patients, a striking similarity in the time of occurrence of the disease was apparent. No patient in our series developed his disease prior to his being in New Guinea or, as later became evident, in the Philippine Islands, for two months. With one exception, each of the 21 patients observed his initial lesion two to five months after his arrival in New Guinea. One of the 21 did not develop his eruption until nine months had elapsed. This inclination for the disease to occur during this interval of time became an important diagnostic factor as it became apparent that the disease manifested itself neither within the first

few weeks nor after the soldier had been in the area for a long time. Thus, the appearance of a skin lesion in the second year of the soldier's tour in the area argued against a diagnosis of atypical lichen planus.

We observed, however, that many of our patients with atypical lichen planus had been in the overseas theater for long periods of time before coming to New Guinea. Although many of these had had tours of duty of varying duration in Australia, the onset of disease seemed to be related to their arrival in New Guinea. Later on in our study we observed many cases in a division which had seen service in the Hawaiian Islands for over a year prior to their being sent to New Guinea. The onset of atypical lichen planus among some of them occurred two to six months from the time they first arrived in New Guinea and, since they soon travelled on from New Guinea to the Philippine Islands, many other cases first became apparent shortly after they arrived in the Philippines. Troops who had been in other areas of the Pacific, where malaria is not endemic, before coming to the Southwest Pacific or to the Philippine Islands, presented their first cases of atypical lichen planus after their arrival in the latter areas.

Geographic Distribution: During the New Guinea phase of the war, it was suggested by some that atypical lichen planus was a disease limited to a particular area of New Guinea itself. Later on, when it was evident that the troops stationed throughout New Guinea added to our series of case-studies it was suggested that perhaps New Guinea alone was the home of this disease. Careful investigation into the location of individuals when the disease appeared, or before it appeared, soon dissipated that impression and the additional suggestion that the disease might have been related to sensitivity to vegetation peculiar to that area. Investigation into the backgrounds of our patients demonstrated that the disease occurred anywhere in New Guinea or the adjoining islands where there were known aggregations of troops. Furthermore, instances of the disease appearing in other theaters of operations, including the China-Burma-India theater and Italy,[1, 2] indicated a more widespread distribution of the disease than had been supposed. The author not only observed patients in the Southwest Pacific but, after the war, when stationed in a General Hospital in the United States, had occasion to see instances of the disease in personnel returned from Burma. The clinical characteristics of the disease in those patients returned from Burma were identical to those observed in his own series of several hundreds in New Guinea and the Philippines.

During the early part of the Philippine campaign there seemed to be a sudden decrease in the number of patients. The expectation that we might find a disappearance of the disease was soon abandoned when as many cases as we had seen in New Guinea seemed to be appearing in troops who had never been in New Guinea. It was apparent then that it was just a question of the newly arrived personnel having to live through the first two or three months before cases of atypical lichen planus appeared among them. The disease among these troops who had never been in New Guinea was identical

to that seen the year before in New Guinea and in so far as we were able to ascertain, this disease had never been described as an affliction of Americans or Filipinos living in the Philippine Islands before the war.

Sex: The disease occurred among male and female personnel with equal severity. The relative incidence in each could not be determined.

Race: Atypical lichen planus was more common in soldiers of the Caucasian race. Few cases appeared among Negro troops, but they had some. One of our very sick patients was an American soldier of Japanese descent.

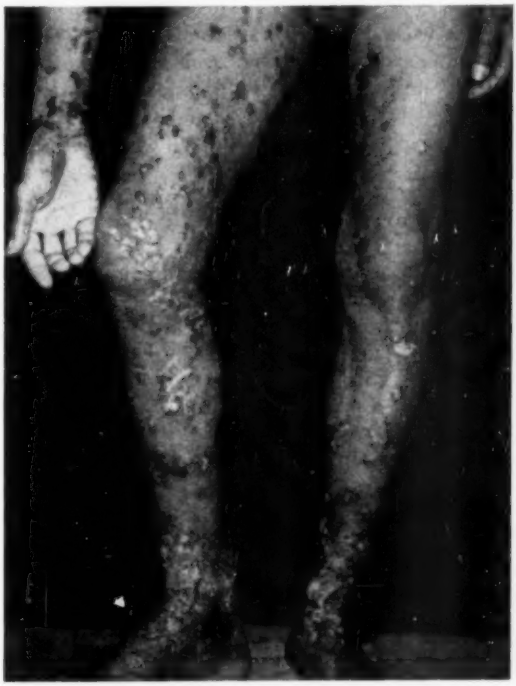

FIG. 2. Case C. D., discrete and confluent hypertrophic lesions in a Chinese-American soldier.

Another one of our patients was an American of Chinese origin. One very sick patient, an elderly Filipino Scout, developed his disease not during Japanese occupation but rather afterwards when he was recalled to service.

Description of Lesion: The characteristic lesion of atypical lichen planus is a well defined, flat-topped, hypertrophic papule, the border of which is irregular and angular. It has a violaceous hue of varying intensity so that some lesions are almost a deep slate blue color. The surface has fine scales and is striated. At first the lesions are discrete but later they tend to

coalesce. When coalescence occurs, the entire skin in the area takes on a markedly lichenified appearance. Other secondary changes occur in the surrounding skin. Outstanding among these is a follicular hyperkeratosis. This is most prominently seen over the upper back and forehead, and associated with it there is often a noteworthy absence of sweating. One-third of the 21 cases previously mentioned had associated eczematoid lesions. Three of those 21 cases had lesions in the scalp, and when scalp lesions occurred alopecia areata co-existed almost invariably. A large number of patients presented an unusual type of fine generalized scaling of the skin which appeared in lace-work pattern. This was particularly striking on the abdomen, chest and back. The earliest lesions seemed to favor the exposed areas of the body, the upper eyelids and the dorsum of the hands being most often involved. Later extension of the disease occurred along the flexor surfaces of the arms and forearms and along the inner aspect of the thighs and upon the dorsum of the feet. The genitalia and perineum were frequently involved, and occasionally the only demonstrable lesions present were on the penis. About one-third of our cases presented oral lesions usually in the form of irregular, non-ulcerated, grayish white patches on the buccal mucosa. Less frequently similar lesions were found on the palate and tongue. Stellate linear fissures in the perianal skin were a characteristic finding. Goldberg [3] reported findings similar to those in the mouth occurring in the anal mucosa in many patients in whom proctoscopic examination was performed.

Occasionally dark grayish-blue pigmentation of soft and hard palate and the nails also occurred concomitantly. This latter finding was likewise found at times in patients not suffering from any cutaneous disease and was attributed to pigmentary changes incident to the taking of atabrine for long periods of time.

No jaundice, hepatomegaly or nervous system involvement were observed. Splenomegaly and lymphadenopathy did not occur in patients in whom significant secondary infection was absent.

Laboratory Findings: In the uncomplicated non-exudative cases there were no regularly observed changes in the leukocyte count, sedimentation rate, urinalysis, blood protein, or A/G ratio determinations. Dantzig and Marshall [4] reported normal liver function tests in a group of patients studied by them. Epstein [5] reported low blood protein and calcium and high blood phosphorus values in his group of 65 patients. He also reported no regularly occurring eosinophilia. Whereas we, too, did not find eosinophilia in the uncomplicated cases, it was a frequent finding in those with the exfoliative dermatitis. Rosenthal [2] on the other hand, reported frequent eosinophilia in atypical lichen planus.

Many of our patients had moderate normochromic and hypochromic anemia. We observed no true aplastic anemia or severe granulocytopenia, though these are known to have occurred. One of our patients with a very severe hypoplastic anemia required multiple transfusions. Most and Hay-

man [6] reported a study on the blood findings in the anemia associated with this disease. They reported granulocytopenia, thrombocytopenia, and normocytic anemia. They likened their findings to those of severe toxic aplasia such as that resulting from benzol.

Pathology

Rosenthal [2] reported an extensive study of the pathology of the disease. He describes the pathological changes as occurring in three separate phases, the acute, subacute, and chronic. In the acute phase, the characteristic

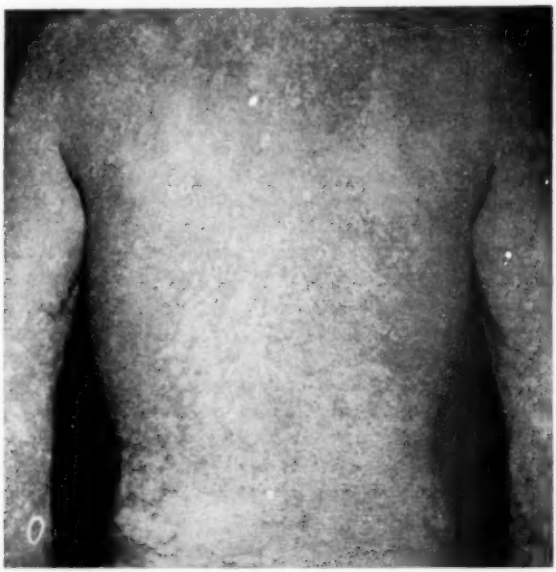

Fig. 3. Case C. C., widespread distribution of atypical lichen planus, demonstrating lichenification, follicular hyperkeratosis, "lace-work" scaling.

changes appeared to be thickening of the stratum corneum, widened hair follicles filled with keratin, acanthosis and marked cellular infiltration with polymorphonuclears, particularly eosinophiles. In the subacute phase there was further widening of the keratin layer. There was less inflammatory infiltration and some histiocytic infiltration. There was also degeneration of the stratum basalis. In the chronic phase the inflammatory reaction was less marked with only scattered inflammatory cells. The featured findings were an acanthosis, plugging of the hair follicles, and increased pigmentation in the basilar layer. This pigment stained with Becker's stain, a non-specific stain for melanin. Two cases of aplastic anemia were observed by Rosenthal,

one of which died of a cerebral hemorrhage after persistent granulocytopenia. The bone marrow in this case was hypoplastic. There was an associated subacute pancreatitis. Degenerative changes were found in the peripheral portion of the liver lobule. Isolated deposition of pigment in the liver was observed. This pigment also stained with Becker's stain and appeared to be the same as the pigment observed in skin with chronic lesions. Goldberg [3] described finding a pigment in the stroma of a biopsied lymph node. The liver presented a greenish fluorescence to ultra-violet ray despite the cessation of atabrine ingestion six months before.

Clinical Course

Patients were kept under our own personal observation for varying periods up to as long as six months. Many of our patients were observed as out-patients, but the greater number were those referred for general hospital care and disposition from many different areas. It became evident as time went on that, with very few exceptions, those who were retained overseas did not show any material improvement. All of our patients who were to be evacuated to the United States were asked to write us after their arrival and report what was happening in so far as their skin lesions were concerned. These reports almost uniformly indicated that slow but steady improvement was to be expected after returning home. At least one patient reported the persistence of eruption as long as 12 months after evacuation from the theater. Though Dantzig and Marshall [4] and Goldberg [3] found no exacerbations of the cutaneous disease when atabrine was administered for a recurrence of malaria, we had a report from one patient who had several recurrences of malaria after leaving our hospital in New Guinea. All of his attacks of malaria were treated with quinine with the exception of one for which atabrine was administered. In the single instance when atabrine was given for his recurrence of malaria there was a severe coincidental exacerbation of the atypical lichen planus.

The hypertrophy of some of the individual lesions was so great that they gave the appearance of cutaneous horns. The nails of the fingers and toes became dystrophic, brittle, and separated from the nail beds. The regression of the individual lesions left in its wake an impermanent pigmentation of the skin and, less frequently, atrophic scarring.

The uninfected cases were afebrile.

From a therapeutic point of view, the cases most difficult to manage were those wherein there was an associated exudative process. Here the problem of nursing and medical care under rigors of tropical living and warfare were heavy. Secondary infection with resulting fever was common. In those instances where large body areas were denuded and exuded plasma, the maintenance of fluid balance and the correction of disturbances in blood chemistry in those patients who suffered severe plasma loss were probably as challenging a problem as any we met.

Of the several hundred cases treated and observed by us in the hospital for an average of six weeks only four showed signs of definite improvement over any significant period of time. All four had had their atabrine withdrawn prior to our being able to make this observation. Many others who likewise had had their atabrine withdrawn showed no improvement while they continued under our observation overseas.

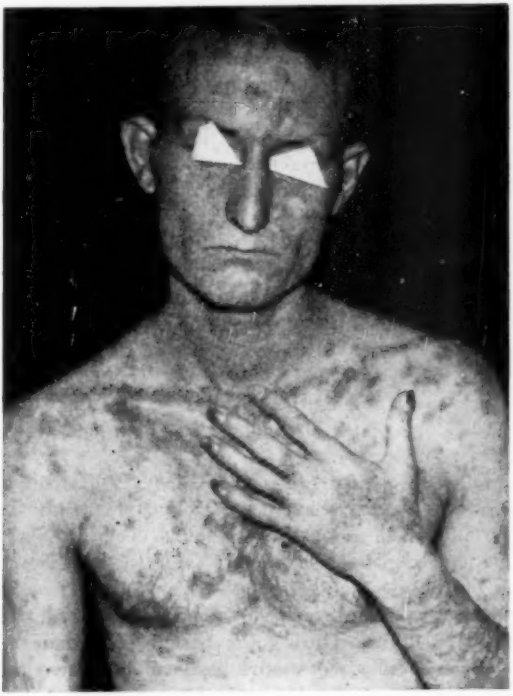

FIG. 4. Case C. W., dystrophy of nails with loss of left index finger-nail. Note, too, the scalp lesions with alopecia areata.

No specific information on the mortality of this clinical triad is available in the literature reviewed. From what has been observed it appears that the mortality was very low and due to complications mentioned before, namely agranulocytosis, aplastic anemia and cerebral hemorrhage.

ETIOLOGY

It is reported[1] that Nisbet and Schmitt first suggested that atabrine might be the cause of this disease. Extensive skin patch-testing by us and

others with atabrine and/or 25 per cent ointment of atabrine in petrolatum gave positive reactions in only a few isolated instances. One would expect that if the disease were the effect of cumulative toxicity many cases would occur *after* the one year period. All of the cases observed by us bore a time relationship to the beginning of suppressive atabrine therapy and not to the arrival of the patients overseas or to their arrival in the tropics or in a particular geographic area. The one constant factor in all of the patients suffering from atypical lichen planus was the ingestion of atabrine in the usual suppressive dose of 0.1 gm. daily. We were unable to find one patient with atypical lichen planus who had been unfaithful in the taking of his atabrine, though this was apt to occur among some of the personnel despite the rigid enforcement of the suppressive use of the drug. There is much to suggest that in addition to a peculiar sensitivity to atabrine there may be one or more additional factors. Among those suggested have been sunlight, nutritional deficiency, and emotional tension. Patients almost uniformly looked and felt better after their hospitalization. In the hospital they received better nursing and medical care for their disease, rest, freedom from the hardships and emotional tension of combat, improved personal hygiene, and removal from the tropical sun. On the other hand, the disease occurred in non-combatant enlisted men and officers as often as in those who were in action. Many of the non-combatants were part of the complement of the very hospital in which they were admitted and treated as patients. These patients were never exposed to the physical and mental rigors of combat. Their food, as well as their facilities for personal hygiene, was unchanged by hospitalization.

In 10 of the first 150 patients that we studied a co-existing labial cheilosis was observed. This always responded to riboflavin administered orally in doses of 5 mg. daily. Coincidental with the disappearance of the cheilosis in two of these patients improvement in the atypical lichen planus was demonstrated. One of these patients had a severe progressive atypical lichen planus. While waiting for transfer to the United States, he developed a severe follicular tonsillitis. During the period of the tonsillitis, his skin condition became markedly worse and he developed, in addition, bilateral labial cheiloses and pressure decubiti over the sacrum, both iliac tuberosities, and medial epicondyles of both femora. On the basis of previously published experiments with riboflavin in decubiti,[7] riboflavin was administered. There occurred a disappearance of the cheilosis and the decubiti, and improvement for the first time in the atypical lichen planus. Continued improvement in his atypical lichen planus was observed for another six weeks when the patient was finally evacuated to the United States. We had hoped to pursue with suitable clinical experiments the possible relationship that might exist with disturbances in riboflavin metabolism as an intermediate step in the development of the disease. The opportunity to develop this phase in our investigation never came, and, as a result, it is mentioned here only as an

isolated observation. No other evidences of specific nutritional deficiency states appeared with significant regularity in our patients.

It was suggested that the subjective improvement or the slowing of the disease that often followed hospitalization might have been due to removal from the excessive exposure to tropical sun. As a basis for this, it has also been suggested that atabrine, a fluorescent acridine dye, might, in some individuals, produce a cutaneous photosensitivity. There is no actual proof to support this interesting hypothesis. One of our patients accepted the rôle of having one hand covered with a gauze bandage in which there had been

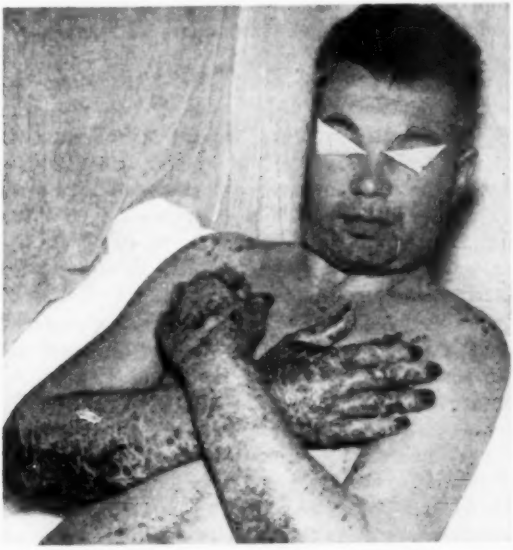

FIG. 5. Case F. E., generalized edema is present. This case of atypical lichen planus is associated with symmetrical exudative eczematoid features. Discoloration of skin and nails due to potassium permanganate.

incorporated some black paper. After six weeks, both the bandaged and unbandaged hand appeared to have progressed equally.

TREATMENT

All patients in whom a diagnosis of atypical lichen planus was made were evacuated to the United States regardless of the extent of the disease. This policy held as well for those patients who had an exfoliative dermatitis. Patients with the eczematoid dermatitis were sent back to duty if, under treatment, the eczematoid dermatitis disappeared and there were no evi-

dences of any lesions suggestive of atypical lichen planus. The rate of recurrence in this group was high, and many of the patients returned to duty had to be rehospitalized later on with the disease in an unresponsive and severe form or, as described earlier, accompanied by lesions of atypical lichen planus. The withdrawal of atabrine did not seem to offer these patients a chance to be cured if they were retained overseas. When we appreciated the rôle of atabrine in the disease, the drug was discontinued. While waiting for evacuation, treatment consisted of skilled nursing care, nutritious diets with liberal multi-vitamin supplements. Local therapy was administered only when exudation was present and this consisted exclusively of wet dressings or soaks. Solutions used for local application consisted of either boric acid, very dilute potassium permanganate, normal saline, or penicillin in saline (500 units per c.c.).

Parenteral penicillin was used in all cases that were grossly infected or in which fever was present.

Remarkable results can be reported from the administration of plasma in the severe exudative lesions regardless of whether or not demonstrable quantitative changes in the blood protein or albumin-globulin fractions existed. Blood plasma was used as often as once or twice a day. When there was an associated anemia of any significant degree whole blood was frequently given in addition to infusions of plasma. No instances of homologous serum jaundice occurred in our experience.

Some patients presented a generalized edema, often unassociated with hypoproteinemia or severe exudation. This edema responded remarkably to plasma infusions. Infrequently the edema was so marked that the only accessible vein for clysis was the external jugular.

The diets were as rich in protein as was possible, and this was supplemented with large amounts of gelatin served in iced fruit juices several times daily. In the exfoliative cases large doses of liver extract were administered intramuscularly as well.

A large hydrotherapy department [8] was maintained in order to provide tubs and basins for soaks and for the preparation of wet dressings. The extent of individual local treatment was solely dependent upon the degree of the exudative process that was going on.

No ointments were used by us in the tropics because it was apparent early that their use aggravated the skin conditions. Occasionally penicillin was used locally for secondary infection with good results but always in solution, excepting the very infrequent occasions when an ointment in a water-soluble base was employed for mild infection in small areas.

For sedation chloral or paraldehyde was used rather than barbiturates. For analgesia codeine was employed rather than salicylates. Arsenicals and bismuth used by others [1] were found not to affect the course of the disease. We had no experience in the use of heavy metals parenterally, nor did we employ radiation therapy in the management of any of our cases.

Summary and Conclusions

1. The history of the disease, atypical lichen planus, was described, and its likely etiological relationship to a peculiar eczematoid dermatitis and a frequently occurring exfoliative dermatitis was discussed.

2. The clinical manifestations, pathology, and laboratory findings were described.

3. Prolonged ingestion of atabrine is considered to be the presumptive basic cause of the disease. Other factors, however, may be secondarily operative in its production.

4. It is the opinion of the author that atypical lichen planus is merely a cutaneous manifestation of a generalized systemic disorder.

5. Few instances of improvement were observed while the patients remained overseas. Because of this, plus the fact that the disease is both disabling and progressive, all patients with atypical lichen planus were evacuated to the United States.

6. Withdrawal of atabrine, and the maintenance of adequate nutrition were applied in all cases. Local therapy was found to be of only temporary value when exudation was present.

7. The value of infusions of plasma and whole blood in the management of the exudation and edema was stressed.

8. Penicillin is a valuable aid in treating those cases exhibiting secondary infection.

Photographs by 4th Med. Museum and Arts Dept., A. U. S.

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CASE REPORTS

PULMONARY EMBOLISM WITH ACUTE COR PULMONALE AND EXTREMELY RAPID VENTRICULAR RATE IN A YOUNG, ACTIVE, APPARENTLY HEALTHY ADULT *

By William F. Renner, M.D., *Baltimore, Maryland*

The problem of venous thrombosis with associated pulmonary embolism has received much attention in the medical literature of recent years. The great bulk of the literature has dealt with venous thrombosis of the secondary or complicating type, that is, venous thrombosis complicating surgery or delivery or occurring in the course of infectious disease or non-infectious systemic disease, particularly cardiac disease with congestive failure. Despite a number of excellent reports on the subject, it is not sufficiently well recognized that venous thrombosis with pulmonary embolism does occur in individuals who have not experienced recent surgery or childbirth, who do not have varicose veins, who have no apparent infectious or non-infectious disease, and who, at the time embolism occurs, are leading a normal active life. In 1945 Hampton, Prandoni, and King reported 10 cases of pulmonary embolism seen in Army personnel at Walter Reed General Hospital, occurring in each case while the individual was at work with no history of cardiac disease or of known phlebitis. The transfer diagnoses in these cases included coronary occlusion,[8] pneumonia, angina pectoris, pericardial effusion, and metastatic carcinoma of the lungs. In no case had the correct diagnosis been made prior to admission to Walter Reed Hospital.

The lack of appreciation by many physicians that venous thrombosis and pulmonary embolism do occur in active otherwise apparently healthy adults and the occurrence of several unusual features in a case recently observed by us are the justification for this report. The patient was referred to The Union Memorial Hospital as a case of paroxysmal tachycardia. Pulmonary embolism was not considered until several hours after admission when further developments and a careful detailed history pointed to venous thrombosis and pulmonary embolism as the underlying disorder. The extremely rapid ventricular rate of 300 to 315 beats per minute is, we believe, the fastest reported in an adult. The presence of a significant autoagglutinin titer raises the question of the possible etiologic significance of this factor in this case.

Case Report

The patient was a 32 year old white salesman for a pharmaceutical company, who was admitted on the House Service, Union Memorial Hospital, December 10, 1947, with the chief complaint of a fainting attack followed by palpitation, four and one-half hours previously. There was nothing of importance in the patient's past

* Received for publication March 30, 1948.
Case from the House Service, Union Memorial Hospital.

history except that since discharge from the Army several years previously he had been imbibing alcoholic beverages heavily. This is mentioned because it is the impression of some that idiopathic venous thrombosis and pulmonary embolism are more common in chronic alcoholics.[12] Review by systems was completely negative except for the information that the patient had had frequent colds during the past winter, the last one six weeks prior to admission.

On December 9, 1947, the patient went to bed at 9 p.m. feeling as usual except that his feet felt unusually cold, for which reason he wore a pair of socks to bed. For three weeks previous, the patient had noticed some stiffness and soreness in his calf muscles upon arising in the morning, which would disappear when he became active. He attributed these symptoms to playing football with his young children during the preceding month. He had noticed no stiffness or soreness in the thighs. The patient arose at 6:30 a.m. December 10 and went downstairs to his desk to work on some company reports. He had been working about 10 minutes when he suddenly became weak and broke into profuse perspiration. He went to the kitchen, wiped off his face, then returned to his desk. A few minutes later he had a chilly

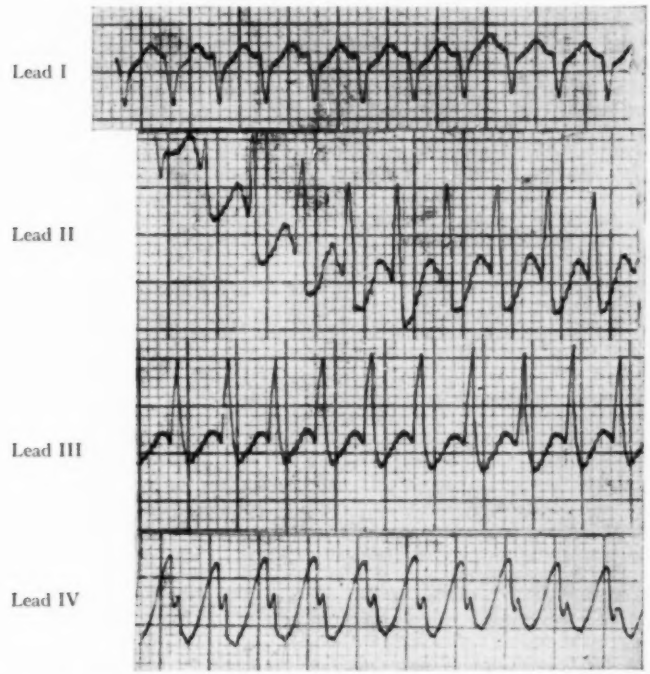

FIG. 1. Electrocardiogram taken two hours after fainting attack and one hour after onset of tachycardia. Rate is 300 to 315 per minute. Note the extreme right axis shift. Because of the extremely rapid rate and the absence of a period of electrical quiescence in the auricles in all leads, the rhythm is interpreted as auricular flutter with 1:1 conduction, although supraventricular tachycardia can not be definitely ruled out. (Compare with figure 2.)

sensation but did not shake, became dizzy, his vision became blurred, and he fell to the floor. He estimates that he was unconscious 5 to 10 minutes. He then crawled on hands and knees upstairs to his bedroom and into bed. Fifteen minutes later, while lying in bed, he noted the onset of rapid forceful beating of his heart followed by mild to moderate dyspnea. An hour later the family physician arrived and took an E.K.G. which showed a ventricular rate of 300 to 315 and a marked right axis shift (figure 1). The patient was given morphine and one cat unit of digifolin parenterally. Various types of vagal stimulation were tried without success. Just before entering the ambulance the patient vomited once. En route to the hospital he noted that his dyspnea had disappeared and that his heart no longer was beating rapidly.

Physical examination immediately upon admission to the hospital was essentially negative. The heart rate was normal. No murmurs were heard, the heart did not appear enlarged, the lungs were clear to auscultation and percussion. The diagnosis of paroxysmal tachycardia was concurred in.

Three to four hours after admission the patient became slightly dyspneic and complained of a sharp pain in the precordial area, radiating to the right chest and to the midscapular area and made worse by deep inspiration. Upon going into the history carefully, it was learned that this pain had come on about an hour after the onset of the tachycardia and had persisted in a dull form up to the present when it had become again accentuated. A cough was now present; no blood was present in the sputum. Physical examination at this time revealed the presence of a short rough sound just to the left of the sternum in the third interspace which was synchronous with systole and which was interpreted to be a pleuro-pericardial friction rub. A loud pleural friction rub was heard anteriorly to the right of the mediastinum at the level of the fourth interspace and extending horizontally to the posterior aspect of the left chest over the left upper lobe. A friction rub was heard also in the left lower axillary area. A few fine crackling râles were heard at both lung bases. Examination of the legs revealed definite tenderness in both calves and a questionably positive Homan's sign on the right. Varicosities were not present.

Laboratory: The white blood cell count on admission was 8,000 with 71 per cent polymorphonuclear cells. Hemoglobin was 89 per cent. Sedimentation rate was 33, uncorrected. An electrocardiogram taken one hour after admission and three and one-half hours after that taken in the patient's home (i.e. four and one-half hours after onset of tachycardia) showed a normal sinus rhythm and a normal axis (figure 2). The rapid reversion of the axis back to normal was in itself considered strong evidence of pulmonary embolism. A third electrocardiogram on the third hospital day showed no important change from the second. A roentgen-ray taken on the day after admission showed perfectly clear lung fields. A repeat film taken on the second day after admission gave evidence of a small embolus in the right base and opposite the fourth right rib anteriorly and the sixth interspace posteriorly. A roentgenogram on the third day after admission showed a reticular density in the outer portion of the mid right lung field, probably due to multiple emboli. The lesion in the right base had cleared. An autoagglutinin titer done one week after admission showed macroscopic clumping out to a dilution of 1:80 (4 plus, 3 plus, 2 plus, 1 plus). An autoagglutinin titer seven weeks later was positive only in a 1:10 dilution (1 plus).

Course: The patient was started on heparin and Dicumarol on the day of admission. On the second day of hospitalization the patient's temperature, which was normal on admission, rose to 101.6° F., returning to normal on the sixth hospital day. After the second hospital day the patient was asymptomatic. A chest plate on the tenth hospital day showed clear lung fields.

Comment: Although it is well recognized that pulmonary embolism may precipitate a paroxysmal arrhythmia, certainly the average physician confronted

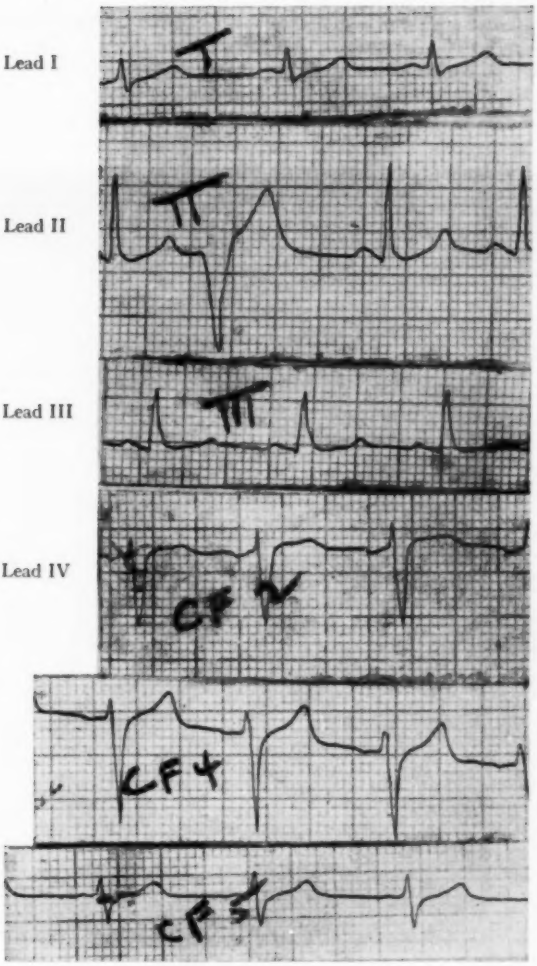

FIG. 2. Electrocardiogram taken four and one-half hours after the tracing shown in figure 1. Sinus rhythm is now present with a rate of 88. Note the marked shift of the axis back to normal, in itself strongly pointing to pulmonary embolism.

with a case of paroxysmal tachycardia in an apparently normal individual is likely to overlook this possibility. The high index of suspicion essential to the diagnosis of many cases of pulmonary embolism must include the paroxysmal arrhythmias. Approximately 300 beats per minute has been considered the upper limit at which the human heart can pulsate. Lyon, in reporting a rate of 313 in a four and one-half week old infant in 1937, reviewed the literature on excessively rapid rates.[13]

He was able to find 16 cases with a rate over 280, ten of which were confirmed graphically. A ventricular rate of 300 was recorded by electrocardiogram in four cases, two of which were in adults. In no case was an electrocardiogram published which showed a rate that exceeded 300 per minute. Katz and White both refer to a rate of 345 in a 10 day old infant as the fastest recorded rate.[11, 18]

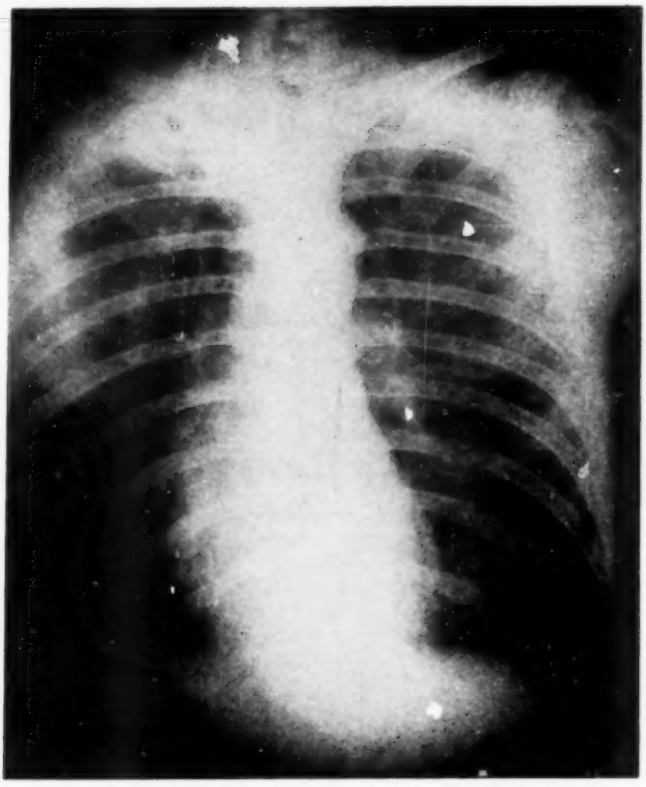

FIG. 3. Chest roentgenogram on the day after attack. Note the dilated heart as compared with figure 5. The lungs were interpreted by the roentgenologist as clear.

To our knowledge, the rate of 300 to 315 in the patient who is the subject of this report is the fastest ventricular rate recorded in a human beyond infancy. The rhythm is considered to be auricular flutter with 1 : 1 conduction.

The etiology of venous thrombosis is still poorly understood. There are three factors which are generally considered important: (1) a local, traumatic, infectious, toxic or preëxisting lesion of the vein wall, (2) relative stasis of the venous blood flow, and (3) changes in the composition of the blood. With re-

gard to the third factor, no single constant abnormality of the blood has been found which can be held responsible in all cases. In the subject of this report local trauma must be considered since the patient was a chronic alcoholic and since he gave a history of playing football with his children for a month prior to his attack. However, he could recall no instance of trauma. Venous stasis may have played a rôle in a patient who occasionally slept cramped in the back seat of his automobile after an alcoholic debauch. In view of the fact that extensive

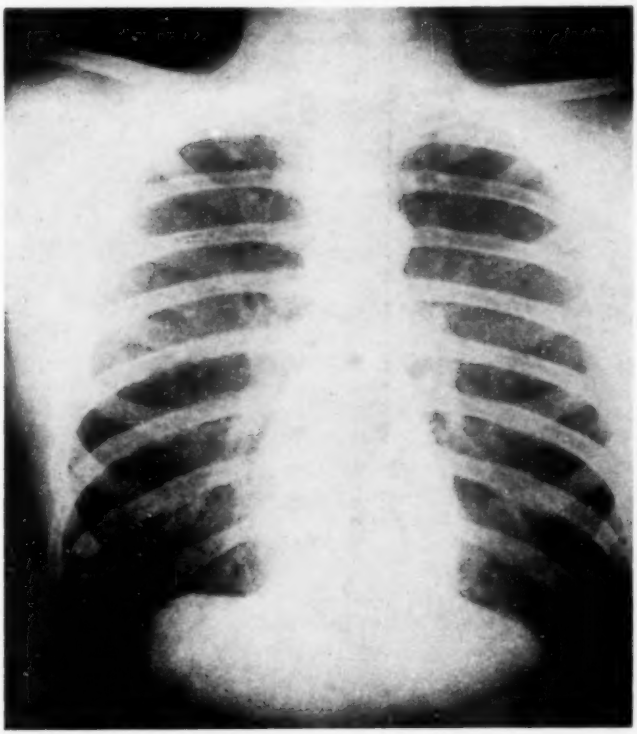

FIG. 4. Chest roentgenogram three days after attack. A reticular density is present in the outer portion of the mid-right lung, suggesting multiple small emboli.

venous thrombosis has been reported in some cases of primary atypical pneumonia with high cold or autoagglutinin titers and in view of the fact that venous thrombosis is thought to be more common in the spring and winter months when respiratory infections are frequent and more common in the northern clinics than in the southern, an autoagglutinin titer was run one week after admission.[16, 17] The titer was 1 : 80 (4 plus, 3 plus, 2 plus, 1 plus), the end point being determined by the presence of macroscopic clumping. Although 1 : 80 is not a very high titer,

it is significant according to the work of Finland et al. at Boston City Hospital.[17] Of 100 patients with no disease examined by these workers, none had an autoagglutinin present in significant titer, that is 1 : 40 or greater. Of 851 patients with various diseases other than primary atypical pneumonia and hemolytic anemia, only 1.2 per cent had autoagglutinins present in significant titer. A titer run on the subject of this report seven weeks after the first was 1 : 10 (1 plus). The

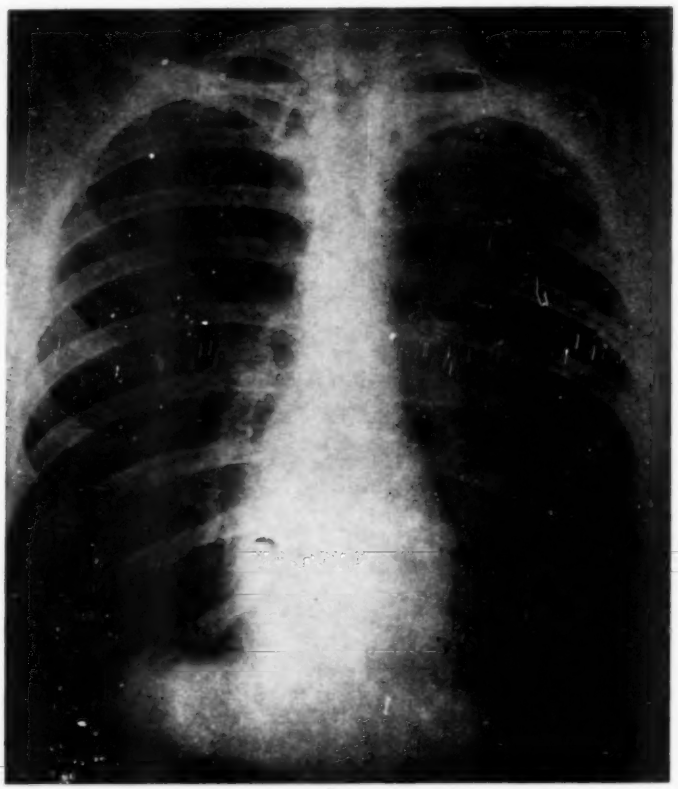

FIG. 5. Chest roentgenogram ten days after attack. Lungs are now clear. Heart has decreased markedly in size. (Compare with figure 3.)

question arises as to whether this patient had a rise in his autoagglutinin titer coincident with one of the frequent respiratory infections to which he is subject and whether such a rise played any rôle in the occurrence of his venous thrombosis and pulmonary embolism. It is of interest that DeTakats has observed, "atypical pneumonia seems to predispose to clotting" of the blood.[16] In an effort to demonstrate activity of the autoagglutinins, one of the patient's hands was immersed

in ice water for one to two minutes. No unusual color change was noted. However, it was noted that, whereas the temperature of the hands of two controls returned promptly to normal, the patient's hand which had been immersed in ice water was distinctly cooler than his other hand one half hour later, and some of the fingers were distinctly cooler than others. We feel that no definite significance can be attached to this.

Summary

1. A case of pulmonary embolism in an active apparently healthy young adult is reported. The high index of suspicion essential to the diagnosis of many cases of pulmonary embolism must include the paroxysmal arrhythmias even in apparently healthy individuals.

2. The ventricular rate of 300 to 315 beats per minute is, we believe, the fastest recorded in a human heart beyond infancy.

3. The possible etiologic significance of cold or autoagglutinins in this case is briefly discussed.

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PARAPLEGIA SECONDARY TO METASTATIC PROSTATIC CARCINOMA TREATED WITH STILBESTROL: REPORT OF A CASE*

By ISIDORE S. EDELMAN, M.D., *Boston, Massachusetts*

INTRODUCTION

TRANSVERSE interruption of spinal cord function occurs relatively infrequently as a result of metastases from carcinoma of the prostate. Bumpus [1] reported that 11 of 1,000 untreated patients with carcinoma of the prostate had symptoms simulating tumor of the cord with some paralysis prior to death. In those patients with cord compression by metastatic tumor and loss of motor power, loss of sphincteric control and associated ascending urinary tract infection, palliation becomes a problem of prime importance.

The beneficial palliative effects of orchiectomy and/or estrogenic therapy in the treatment of advanced prostatic carcinoma are well known.[2, 3, 4, 5, 6] However, the response of neurologic complications to this type of therapy has been observed less frequently. In at least five cases previously reported, considerable relief was obtained by hormonal therapy.[4, 5, 9, 10] The following is an additional case of this kind.

CASE REPORT

The patient, a 66 year old white male, was admitted to this hospital on June 24, 1947 because of generalized weakness and pain in the region of the right ischium. His symptoms began approximately six months prior to admission with severe lower abdominal cramps and anorexia. During the next four months, he developed urinary frequency, urgency and dysuria. He had been admitted to another hospital in May 1947, where the prostate was found to be hard, fixed and enlarged. Roentgen-ray examination revealed a left pleural effusion and metastatic involvement of the vertebrae, ribs, skull and pelvis. A transurethral resection of the prostate was performed because of urinary retention. The pathological report on the tissue obtained was "adenomatoid hyperplasia of the prostate." There had been a weight loss of 40 pounds. The patient was transferred to this hospital for further care.

Physical examination revealed an emaciated and pale elderly male. His blood pressure was 110 mm. Hg systolic and 65 diastolic. The pulse rate, respiratory rate and temperature were all normal. The only findings of note were tenderness over the hips, pitting edema of both ankles and a stony hard, asymmetrically enlarged prostate. The neurological examination was negative except for increased deep tendon reflexes in all extremities.

On admission, the laboratory findings of significance were an alkaline phosphatase of 22.7 Bodansky units, an acid phosphatase of 5.0 Gutman units, a red blood count of 2.38 million cells per cu. mm. and a hemoglobin of 7.9 grams. The sternal marrow was found to be aplastic and to contain tumor cells in clumps. Serum Kahn, blood urea nitrogen, fasting blood sugar, total plasma proteins, and urinalysis were all within normal limits. The urine was negative for Bence-Jones protein on three occasions. An electrocardiogram showed left axis deviation. Roentgen-ray examination of the skull revealed a 2 cm. isolated zone of radiolucency in the parietal region. Extensive osteoblastic changes were noted throughout the dorso-lumbar spine, ilia and sacrum. Rarefactive areas were seen in the pubis and ischium. Sev-

* Received for publication February 7, 1948.
From the division of Neoplastic Diseases, Montefiore Hospital, New York, N. Y.

eral of the lower ribs showed sclerotic changes and the left costophrenic sinus was obliterated. Intravenous pyelography was negative except for a large oval filling defect in the floor of the bladder presumed to be due to an enlarged prostate. Barium enema and gastrointestinal series were essentially negative.

On July 18 an acid phosphatase of 12.0 G.U. and on August 1, one of 10.2 G.U. were reported. A diagnosis of carcinoma of the prostate with extensive bony metastases was made and the patient was started on pituitary irradiation as an experimental procedure. From July 31 to August 19, the patient received 3,000 roentgens delivered by cross-firing through three fields to the pituitary gland. The patient failed to improve. He complained of increasing pain in the hips and low back. On August 28, weakness of the legs was noted. By the September 2, a marked paraparesis of the lower extremities and an absence of pain perception corresponding to a level of D–8 had developed. In addition, marked hyperreflexia at the knees and ankles with ankle clonus and positive Babinski signs bilaterally were found. Lumbar puncture performed at L 4–5 showed considerable block. As can be seen from figure 1, there was a prompt rise in spinal fluid pressure on applying abdominal pressure but practically

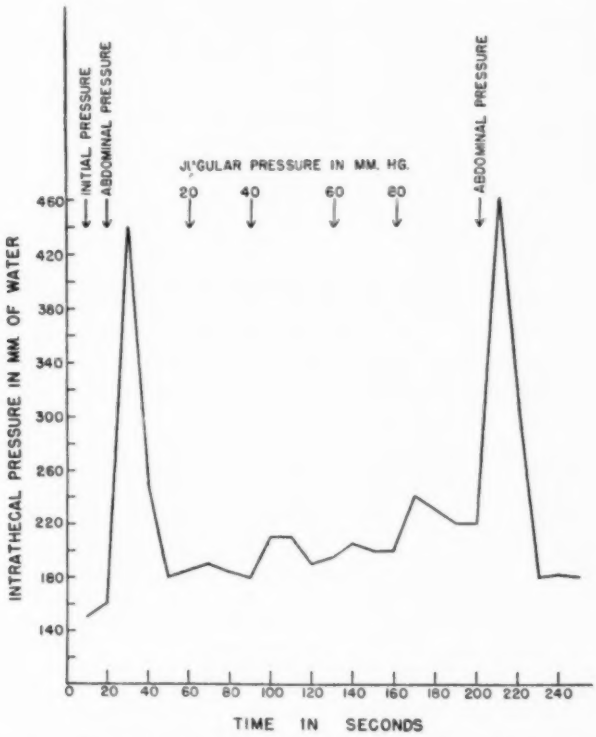

FIG. 1. September 3, 1947. Incomplete block prior to stilbestrol therapy. Spinal fluid manometrics measured with a water manometer and pressure applied by a sphygmomanometer with the cuff around the neck.

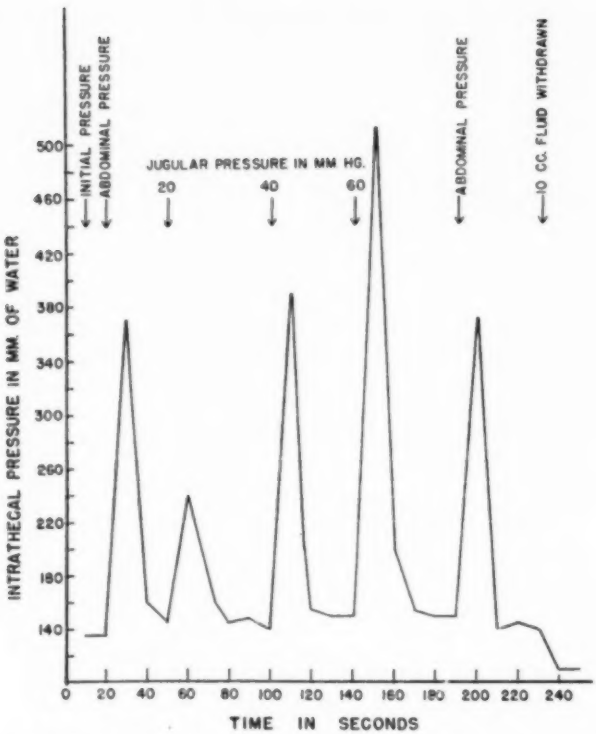

FIG. 2. October 14, 1947. Open manometrics after stilbestrol therapy. Spinal fluid manometrics measured with a water manometer and pressure applied by a sphygmomanometer with the cuff around the neck.

no rise when the neck veins were compressed by means of a sphygmomanometer cuff raised to a pressure as high as 80 mm. of mercury. These findings are consistent with a partial block to the free circulation of spinal fluid. Examination of the fluid revealed xanthochromia, a 1 plus Pandy reaction, a protein of 170 mg. per cent and only a few cells. Roentgen-rays of the dorsal spine failed to show collapse of any of the vertebral bodies. A neurosurgical consultation was obtained, and it was felt that laminectomy for decompression was not indicated. By September 5 the paraparesis progressed to a paraplegia and the patient was started on 15 mg. of stilbestrol per day. Ten days later the patient began to have a return of motor power in his legs. By September 26 he had a return of pain perception and could move his legs almost perfectly. On September 29 his acid phosphatase decreased to 0.2 G.U. A lumbar puncture performed on October 14 yielded normal manometrics. As contrasted to figure 1, it can be seen from figure 2 that there is an immediate and sharp rise in intra-thecal pressure with pressure applied around the neck of 20, 40 and 60 mm. of mercury. In addition, the prompt fall in spinal fluid pressure to base levels on removal of neck pressure is indicative of an unobstructed spinal fluid circulation. At this time, the patient had relief of pain, a decrease in anorexia and a striking increase in his feeling

of well-being. The patient could stand but not walk unassisted. Ankle clonus and the positive Babinski persisted. On digital rectal examination there seemed to be a decrease in the size of the prostate. The patient was discharged on October 30, 1947. He was seen on November 5, 1947 and continued to be improved.

Discussion

The diagnosis of prostatic malignancy was based on the physical characteristics of the gland, the fairly typical osteoblastic metastases and acid phosphatase values above 10 units. The striking therapeutic response to estrogenic therapy and fall in the acid phosphatase values to normal supports the diagnosis. Although other conditions can give small increases in serum acid phosphatase levels, a value greater than 10 units is considered to be diagnostic of prostatic carcinoma.[9]

The pathogenesis of the paraplegia seems to be fairly clear. The clear cut evidence of a spinal fluid block without collapse of any of the vertebral bodies indicates that a soft tissue mass was compressing or invading the spinal cord. That this mass was metastatic from the prostate is supported by the considerable symptomatic relief, the open manometrics and return of spinal fluid protein to normal, with stilbestrol therapy.

Table I

Pertinent Laboratory Data before and after Stilbestrol Therapy

	Alkaline Phosphatase Bodansky Units	Acid Phosphatase Gutman Units	Spinal Fluid Protein
7/18/47	16.8	12.0	
8/ 1/47	16.6	10.2	
8/28/27	Onset of Paraplegia		
9/ 4/47			170 mg. %
9/ 5/47	Stilbestrol Therapy Started		
9/29/47	17.7	0.2	
10/13/47	22.8	1.7	
10/14/47			31 mg. %

The time relations and chemical changes indicated in the above table suggest that the relief of the neurologic symptoms came about as a direct result of an inhibiting effect of stilbestrol on the tumor growth in the spinal canal.

Clarke and Viets [10] reported a very similar case with objective evidence of relief of a spinal fluid obstruction. As far as we know this is the second time that objective evidence of relief of a block within the spinal canal by hormonal therapy has been demonstrated. Of greater importance, however, is the palliative effect obtained. In this instance, a patient with advanced and widespread cancer, with severe pain, completely bed-ridden and paralyzed from the waist down, was enabled to leave the hospital free of pain and able to move his legs.

Summary

A case of paraplegia secondary to metastases from a carcinoma of the prostate is reported. Relief of symptoms and of a spinal fluid block occurred after administration of stilbestrol. The importance of palliation in this type of case is stressed.

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HYPERSENSITIVITY TO FOLIC ACID*

By Dana C. Mitchell, M.D., R. W. Vilter, M.D., F.A.C.P., and C. F. Vilter, M.D., *Cincinnati, Ohio*

Synthetic folic acid (pteroyl glutamic acid) has been used extensively in clinical investigation since November 1945 following reports of its effectiveness in the anemia of pernicious anemia, sprue and nutritional macrocytic anemia.[1, 4] It has been available for general use during the past years and although it has been helpful in controlling the anemia of persons with pernicious anemia who developed hypersensitivity reactions to liver extract, it has failed to prevent the neurologic complications of pernicious anemia.[5] Up to the time of writing hypersensitivity reactions to folic acid have not been noted though some persons who have received between 50 and 250 mg. intravenously have complained of flushing and tingling sensations in the face and extremities and other unpleasant vasomotor symptoms.[3]

Recently we have observed a patient who developed maculopapular dermatitis during a course of folic acid given orally and a severe anaphylactoid reaction later following the intravenous administration of 50 mg. The case is being reported since we are not aware that a similar reaction has occurred following the administration of folic acid.

Case Report

A 35-year-old white woman was admitted to the Medical Service of the Cincinnati General Hospital on April 17, 1947 with a diagnosis of granulocytopenia which had followed the administration of thiouracil. The patient had been treated in the

*Received for publication August 18, 1947.

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Out-Patient Dispensary for thyrotoxicosis and thyrotoxic heart disease since April 1943. Three courses of thiouracil had been administered during this time with a reduction in basal metabolism and temporary improvement in cardiac function. On April 24, 1946 the patient had developed a mild leukopenia during one of the courses of thiouracil and was given 5 mg. folic acid orally three times a day in an attempt to combat it. She took both thiouracil and folic acid for two weeks. When, however, a maculopapular erythematous and pruritic rash appeared over her anterior chest wall and the extensor surfaces of both forearms, she discontinued the folic acid. Within 36 hours the pruritus disappeared and the skin rash had begun to clear even though she was still taking thiouracil. Later the thiouracil was discontinued since the leukopenia persisted and the thyrotoxic symptoms had abated. On April 3, 1947 thiouracil therapy was reinstituted, 0.2 gram three times a day because of recurrent thyrotoxic manifestations. On April 14, 1947 she noted a severe sore throat and an itching maculopapular rash over the arms and shoulders. She discontinued the thiouracil, the rash began to clear but the throat became progressively more painful.

The patient's past history did not reveal any suggestion of allergic tendencies until about three years before admission. At this time she developed recurrent generalized maculopapular eruptions which she attributed to the ingestion of tomatoes, pork or oranges, to contact with woolen blankets, many common soaps and most face powders. During a previous hospitalization she had developed dermatitis following the administration of phenobarbital and an erythematous pruritic rash and shortness of breath shortly after the administration of nembutal and aspirin.

The patient was acutely ill, her temperature was 104° F. and her pharynx was fiery red, edematous and covered with purulent exudate particularly over the tonsils. She had difficulty in swallowing, moderate trismus, and mild cardiac failure with auricular fibrillation. The white blood cell count was 2000 and the differential count 96 per cent lymphocytes and 4 per cent monocytes. The bone marrow showed 9 per cent myeloblasts but no more mature granulocytes. The erythrocyte series was essentially normal and megakaryocytes were present in normal numbers.

During the first week her temperature ranged between 101 and 104°. Penicillin and general supportive measures were ineffective in controlling the throat infection. Since the patient's course was steadily downward and since she showed no evidence of recovery of myeloid elements in the peripheral blood, all types of reputed bone marrow stimulants were given consideration. Folic acid was selected because there had been no reports of hypersensitivity reactions following its administration even though the evidence from the literature and our own experience did not indicate that it would be effective in this type of toxic granulocytopenia.[2] She was given one dose of 50 mg. of synthetic folic acid intravenously on April 24, 1947. There was no objective reaction to this initial injection but the patient stated later that she had noted slight flushing of the face and dizziness. On the following day a second dose of 50 mg. synthetic folic acid was administered intravenously. Immediately after the injection had been completed the patient suddenly became dyspneic, orthopneic, and extremely anxious. She sat up in bed, grasped her chest, and complained of severe substernal oppression. Her face became fiery red, then a livid purple. The pulse rate became extremely rapid (170 to 190 beats per minute) and could not be palpated at the wrist. Her respirations increased to 40 per minute. Blood pressure readings were not taken. The extreme dyspnea and orthopnea lasted about five minutes. Thereafter breathing became easier and orthopnea gradually disappeared. After 10 minutes the patient was able to lie back in bed and the cyanosis of the face had decreased.

Two days following this reaction and again 16 days later intradermal skin tests were carried out with the original solution of folic acid (No. 1) which had produced the reaction and similar material from a second stock bottle of folic acid (No. 2).

In the first test the control solution was physiologic saline and in the second, a 1 per cent solution of sodium bicarbonate, the solute for the folic acid. In both instances positive skin reactions were obtained to the solutions containing folic acid (table 1). Attempts to demonstrate precipitins for folic acid in the patient's serum were unsuccessful.

The patient remained critically ill until April 30, 1947 in spite of the use of both penicillin and streptomycin. Thereafter her temperature fell, infection cleared and bone marrow studies revealed an increase in myeloid elements with maturation arrest at the B myelocyte stage. On May 3, 1947, the sixteenth hospital day, 21 per cent

TABLE I

Reaction to Intradermal Tests with Folic Acid and Solutions of Physiologic Saline and Sodium Bicarbonate

April 27, 1947	5 minutes	10 minutes	15 minutes
Folic acid No. 1	Erythema, 3.5×2 cm.	Erythema, 3.5×4 cm. with pseudopods	Erythema 3.5×3 cm., pseudopods receding
Normal saline	Negative	Negative	Negative
May 13, 1947	**5 minutes**	**10 minutes**	**15 minutes**
Folic acid No. 1	Erythema, 2.5×3.5 cm.	Erythema, 3.5×3.5 cm. with pseudopods	Erythema, 2.5×1.75
Folic acid No. 2	Erythema, 2.5×4 cm.	Erythema, 2.5×4 cm., large pseudopods	Erythema, 2.5×2.25
1% sodium bicarbonate solution	Negative	Negative	Negative

young polymorphonuclear leukocytes were found in the peripheral blood. From that time on her recovery was rapid. Polymorphonuclear leukocytes returned to normal and the patient was discharged in good condition on June 4, 1947.

SUMMARY

An instance of a severe anaphylactoid reaction following the intravenous administration of folic acid is reported. The patient had a history of sensitivity to many common drugs and had had an episode of dermatitis following a previous course of folic acid administered orally. Sensitization is presumed to have occurred at this time.

Such a reaction to folic acid must be quite rare since the drug has been administered orally and parenterally many times in the last few years without a report of a similar reaction.

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DIAGNOSTIC FEATURES OF SPLENIC CYSTS WITH CASE REPORT AND REVIEW OF THE LITERATURE*

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Splenic cysts occur infrequently in the human body. They were first mentioned by Andral[1] in 1829 in an autopsy report. Pemberton,[2] in a review of splenectomies at the Mayo Clinic, found four cysts in 800 cases. Sweet[3] more recently reviewed the literature and observed 148 cases of all varieties of cysts up to 1941. This low incidence is no doubt the cause of our paucity of knowledge regarding the clinical features. After reviewing the literature and comparing the essential findings of our case with those reported, we were impressed, however, with the remarkable similarity of the clinical and roentgenological pictures of splenic cysts. The diagnostic features are usually quite evident and afford a basis for a preoperative diagnosis. Discussion of the findings in the case here reported will serve as a general review of this subject.

Classification

Several classifications of cysts have been outlined. Of these many are confusing and offer little aid to the clinician. McClure and Altmeier[4] divide them into true and false cysts. The true cysts have a specific secreting membrane either epithelial, endothelial or parasitic in nature. The false cysts have a dense hyaline fibrous tissue or a layer of condensed splenic tissue. The contents of the latter may be hemorrhagic, serous, inflammatory or degenerative. Lubarsch[5] divides them into lymphatic cysts with clear fluid, hemorrhagic cysts with bloody contents, and dermoid cysts with sebaceous substance. Paul[6] classifies them into hydatid; multiple serous cysts, usually associated with polycystic disease of the kidney; and single or dermoid, epidermoid, serous or blood cysts.

A histological classification has little to offer. Some writers will classify cysts according to contents, others according to etiology, and still others depend

* Received for publication April 2, 1947.
From the Medical Service, Queens General Hospital, Dr. James R. Reuling, Director.

on the pathology. Fowler [7] divided all cysts into primary and secondary, and his classification, outlined below, is that which is most often used:

Primary 21 per cent	Congenital—originate by infoliation and dilatation
	Traumatic
	Inflammatory
	Neoplastic—dermoid, epidermoid, lymphangioma
	Parasitic—echinococcal
Secondary 79 per cent	Trauma
	Degeneration
	Inflammation

Case Report

A married female 19 years of age, was admitted to the medical service of the Queens General Hospital on May 25, 1946, with a complaint of pain in the left chest, together with malaise, anorexia, and a weight loss of 18 pounds in three months. Two weeks before admission she began to experience severe stabbing pains in the left lower antero-lateral thoracic region. At the same time she noted a diffuse tender swelling in the same area. Deep respiration, coughing, and sneezing accentuated the pain. She ran a low-grade fever and developed a slight cough at the same time. The pain radiated to the back from the epigastrium along the infracostal border and

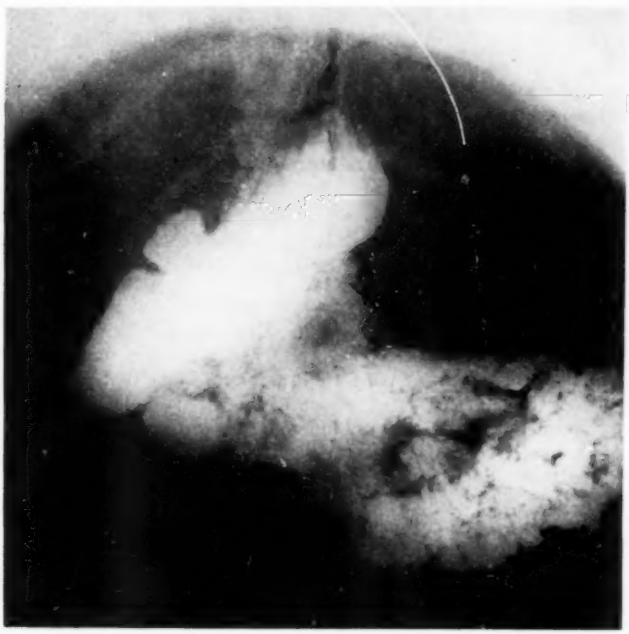

Fig. 1. Displacement of stomach to the right of the midline.

to the left shoulder. She was placed on sulfa drugs and penicillin by her local physician, but as the swelling persisted hospitalization was advised.

The past history was essentially negative except for a normal delivery two years previously. Family history was non-contributory.

Physical examination revealed a well-developed and nourished young girl, complaining of pain in the left lower chest and avoiding all motion. Positive findings were limited to the lower thorax and abdomen. There was slight diminution of breath

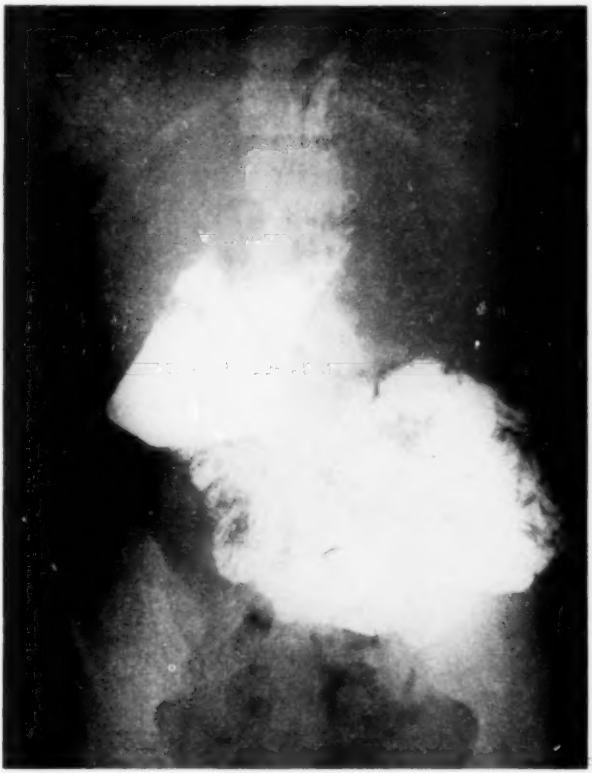

FIG. 2. Displacement of stomach to right by cyst of spleen.

sounds in the left base posteriorly and a diffuse swelling presented itself anteriorly in the left upper quadrant, which seemed soft and cystic. The outlines of the spleen and liver were not palpable. Moderate tenderness was elicited over the mass, which was about half the size of a grapefruit.

Laboratory studies revealed a normal leukocyte and differential count on three occasions, with 3,400,000 red cells and 8 gm. of hemoglobin. Serologic test for syphilis, blood proteins, urea nitrogen, cephalin flocculation, and alkaline phosphatase

were all normal. Platelets numbered 92,000, and bleeding and clotting times were normal.

Fluoroscopy revealed a clear left costo-phrenic sinus but a fixed left diaphragm. A roentgenogram of the chest was normal. Gastrointestinal studies showed no intrinsic pathology but the stomach was moderately displaced to the right and to a lesser extent anteriorly by an extrinsic mass (figures 1, 2, 3). The colon studies showed no displacement. Genito-urinary films revealed a congenitally displaced left kidney

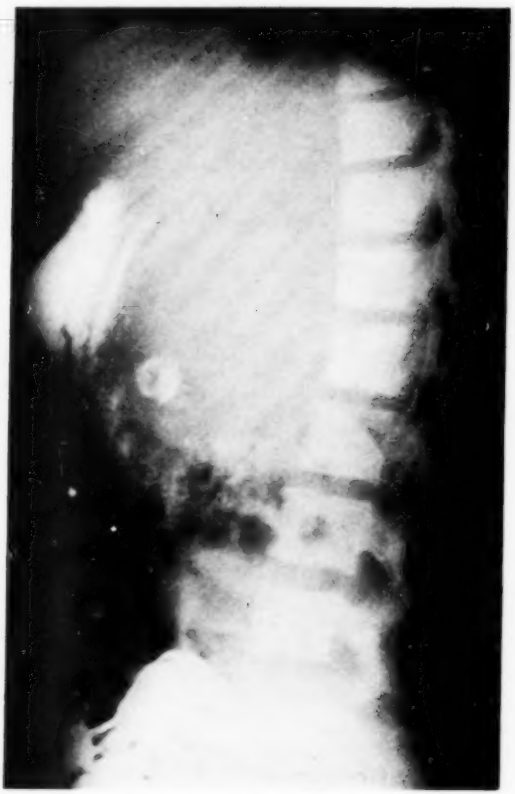

FIG. 3. Anterior displacement of stomach as seen in lateral view.

with a double pelvis lying to the right of the vertebral column. It was felt the patient had a congenital horse-shoe kidney, atopic and located on the right, which condition was probably unrelated to the splenic cyst (figure 4).

On the twenty-second hospital day the patient was taken to the operating room, where a large cystic spleen was found (figure 5). Approximately 1.000 c.c. of a brownish fluid were aspirated before removal of the viscus. The fluid was sterile and had a specific gravity of 1.028 and a leukocyte count of 59,000 cells, 85 per cent being polymorphonuclear leukocytes and 15 per cent lymphocytes.

Post-operatively the patient did well. The platelet count was followed for a week post-operatively, rising to a high of 212,000 on the seventh day.

The pathological report by Dr. A. Angrist noted the following: "Specimen consisted of a spleen weighing 610 gm. There was an incision into a loculated cyst filled with thick bloody fluid. The capsule was smooth, dark red in color and contained several hard grayish calcified zones. On section the greater part of the spleen was

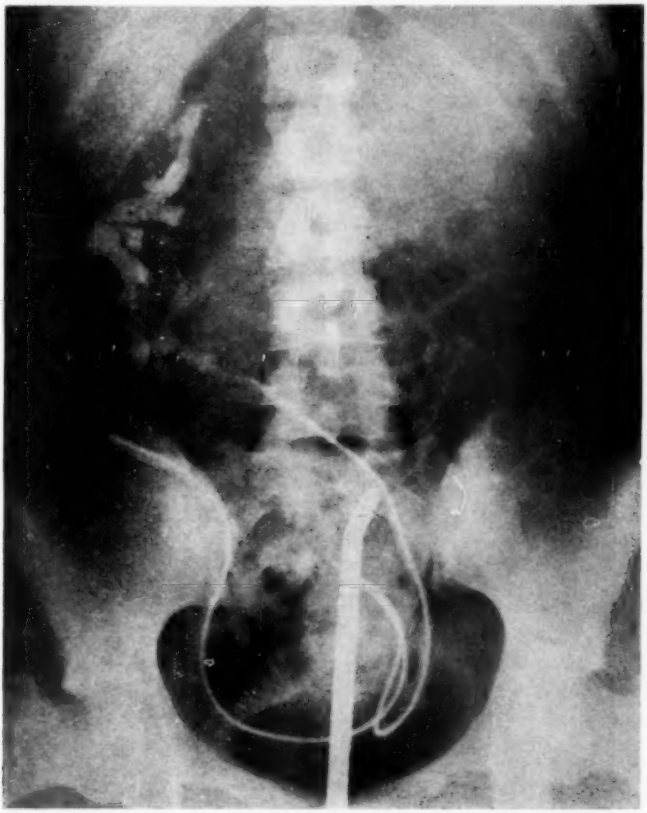

FIG. 4. Displaced left kidney to the right of the vertebral column.

made up of loculated large cystic areas lined by a calcified tissue. The impression was that we were dealing with a splenic cyst with a connective tissue wall that showed fibrosis, atheromatosis and slight calcification."

DISCUSSION

The etiology of splenic cysts is unknown, though several independent factors are suspected. The presence of these tumors in women of childbearing age has

been commented on by DeLee,[8] McClure [4] and Denneen.[9] DeLee suggests that the cyclical hormone changes occurring during menstruation and pregnancy alter the size and congestion of the spleen, and that trauma during the phase of enlargement and congestion may be sufficient to induce hematoma or cystic changes. Trauma alone is considered significant in many of the reported cases. Cystic

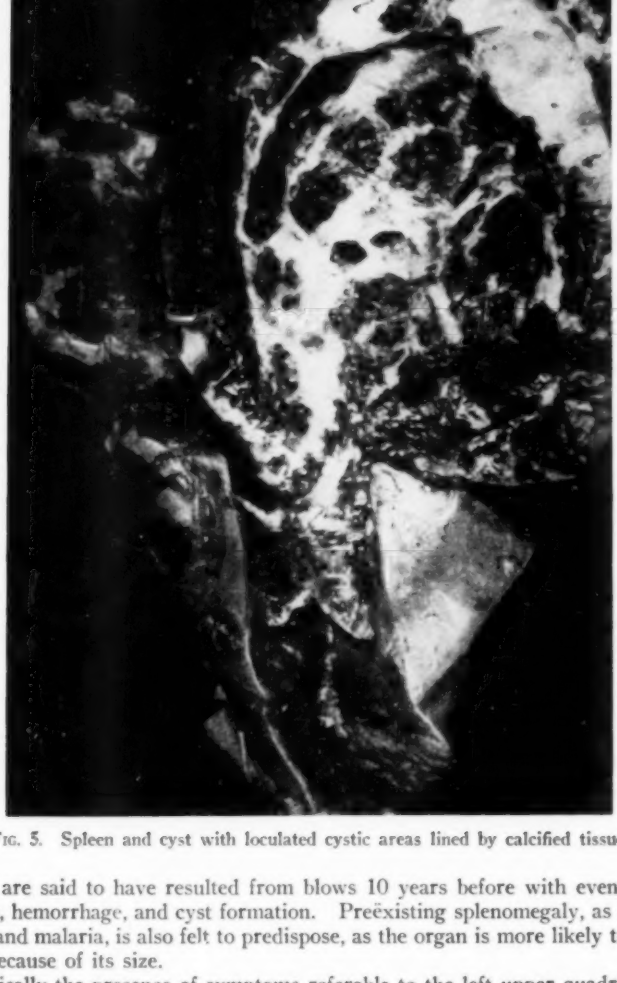

FIG. 5. Spleen and cyst with loculated cystic areas lined by calcified tissue.

spleens are said to have resulted from blows 10 years before with eventual infarction, hemorrhage, and cyst formation. Preëxisting splenomegaly, as a result of lues and malaria, is also felt to predispose, as the organ is more likely to be injured because of its size.

Clinically the presence of symptoms referable to the left upper quadrant and

just under the left costal margin are significant. The presence of pain depends on the size of the mass. A large one may cause the patient to complain of a heavy dragging pain; a smaller one may be less disturbing. The mass usually is soft and cystic. The spleen may or may not be outlined, again depending on the size of the mass. The presence or absence of fever is another problem which offers no help. If the cyst is of the inflammatory variety a febrile reaction will obtain. The presence of a fixed left diaphragm with diminished breath sounds is characteristic. The splenic mass displaces the immediately surrounding structures, notably the left diaphragm, the stomach, and the splenic flexure and transverse colon. Pancreatic and ovarian cysts may offer a problem but they do not offer resistance to the left costal margin. Ovarian cysts may be traced into the pelvis, whereas splenic cysts enlarge, transversely. The large leukemic spleen also grows down towards the pelvis and we do not see the spreading of the ribs and the involvement of the left diaphragm. These clinical findings, if considered with the roentgen visualizations, make the diagnosis obvious.

Roentgenologically, a splenic mass growing anteriorly and under the costal margin causes visceral displacement, and elevates the left diaphragm to impair the latter's motion. The barium-filled stomach is displaced to the right, the colon is pushed down and to the right. The left kidney may also be displaced downward. Calcification occurs frequently enough in these splenic tumors to have been commented upon by Bachman,[10] Gallagher,[11] Jamison,[12] Shawan,[13] and Snoke[14] in their case reports. Ostro and Makover[15] feel that any spleen that grows downward and anteriorly will not displace the neighboring organs as will a splenic cyst. Benton[16] feels that downward displacement of the splenic flexure is almost pathognomonic of large cysts of the spleen.

The laboratory is of no help in the differential diagnosis except in a negative fashion.

Therapy is specific. All cases are amenable to surgery and usually do very well.

Summary

1. A case report of a patient with a splenic cyst is given because of the relative infrequency of the condition.

2. The etiology of splenic cysts is still obscure.

3. The diagnostic features of a palpably enlarged tumor, paucity of symptoms, occasional calcification, pathognomonic roentgenological findings are stressed.

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TROPICAL EOSINOPHILIA WITH REPORT OF A CASE TREATED WITH PENICILLIN *

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SEVERAL articles and case reports have recently appeared in the literature concerning this disease which was first described in 1919,[5] and was given the name tropical eosinophilia by Weingarten [1] who in 1943 reported 81 cases. Since then all reported cases have been successfully treated with organic arsenical drugs.

The disease is characterized by lassitude, fever, anorexia, weight loss, and cough. The latter occurs characteristically in the early morning hours between 1 and 5 a.m. and is accompanied by asthmatic wheezing. Later dyspnea and orthopnea develop. A marked eosinophilia is present, sometimes reaching as high as 70 to 80 per cent, together with a leukocytosis. There is a relative as well as absolute increase in eosinophiles, all of which appear to be normal mature forms. If the disease remains untreated, it becomes chronic.

Weingarten's series of cases was observed in the coastal regions of India around Bombay. One of them fortuitously contracted syphilis and was given specific treatment with neoarsphenamine, following which his hypereosinophilia subsided to normal. As a result of this observation, Weingarten treated similar cases with the same drug, after which all apparently became well.

The only other conditions showing such a high eosinophilic count are periarteritis nodosa and eosinophilic leukemia. However, in tropical eosinophilia, immature forms of eosinophiles are not found and the course is usually benign.

In 1944, Emerson [2] reported a case in a young naval officer who had lived in India before the war, where he had suffered with asthma and sinusitis. He was found to have a leukocytosis with 20 per cent eosinophiles which later arose to 78 per cent following the incision and drainage of a staphylococcic liver abscess. He was successfully treated by the oral administration of carbarsone.

Parsons-Smith [3] in 1944 reported a case he observed in an English airman stationed in Egypt. Symptomatic treatment for asthma gave no relief. At this

* Received for publication June 18, 1947.

time Weingarten's article arrived in the middle East, and neoarsphenamine was then employed with dramatic success.

In 1945 another case was reported by Hirst and McCann [4] in another naval officer serving in the Pacific area, who suddenly developed severe asthma accompanied by headaches. He had never been in India and his overseas duty had been in Central America and the central and south Pacific islands. His asthmatic symptoms had their onset two years previously in Samoa. He was found to have a leukocytosis of 15,000 cells per cu. mm. with a hypereosinophilia up to 72 per cent, which later rose to 82 per cent. The sputum was loaded with eosinophiles. No parasites could be found. His response to neoarsphenamine therapy was again dramatic, five doses four days apart resulting in prompt and complete cure.

Van der Sar and Hartz [5] in 1945 reported their experiences with cases of tropical eosinophilia observed in Curaçao, and conclude that they have demonstrated the relationship between this disease and filariasis since they were able to demonstrate microfilariae in a biopsied lymph node from a typical case of tropical eosinophilia.

Apley and Grant [6] in 1945 reported on five cases observed in England in servicemen invalided back from the Middle East, all of whom promptly responded to arsenical therapy. They further discussed the possible relationship between Loeffler's syndrome, tropical eosinophilia, periarteritis nodosa, and bronchial asthma, which they classify together under the term "E P syndrome," meaning eosinophilia with pulmonary infiltration.

In 1946 Irwin [7] reported two additional cases of tropical eosinophilia originating in the southwest Pacific which also responded to arsenical therapy. He calls attention to the possibility of this being caused by filariasis, as suggested by Van der Sar and Hartz, inasmuch as both of his patients had spent considerable time in an area where *Wuchereria bancrofti* is prevalent. However, repeated examinations of the blood at all hours revealed no microfilaria and the biopsies from muscle, lymph node, and bone marrow showed no filariae although both patients had positive skin test reactions to *Dirofilaria immitis* antigen. He pointed out, however, that false positives are common in the use of this antigen.

It has thus been established that arsenical compounds are, specific in the treatment of tropical eosinophilia and that prompt and complete recovery follows their use. As far as we can determine it has never been effective in the other conditions characterized by marked eosinophilia. The effect of penicillin in tropical eosinophilia has not to our knowledge been reported previously. It is for this reason that we decided to test its action in this disease.

Case Report

The patient, a 23 year old Marine sergeant, was admitted to a naval hospital on February 11, 1947, complaining of nocturnal cough, progressive loss of weight amounting to 28 pounds during the past six months, and general malaise. He stated that he had been perfectly well and healthy until after his return from the western Pacific (Japan) in March, 1946. One month later he noted the onset of a deep nocturnal cough productive of a moderate amount of thick, tenacious, dark-colored sputum. Although the cough was present to some extent during the day it usually became worse after going to bed and would awaken him around 2 a.m. He would usually vomit after a particularly severe coughing spell, often being unable to retain his break-

fast. He had never coughed up any parasites and denied hemoptysis. His symptoms gradually became worse so that by November, 1946 he wheezed audibly on respiration and noticed dyspnea for the first time. Often he was unable to remain lying down due to the dyspnea, which became progressively worse. At the time of his return from overseas he weighed 170 pounds, as compared with 140 pounds at the time of his hospital admission. He had not been aware of any fever, night sweats, diarrhea, or genito-urinary symptoms suggestive of filariasis, or other parasite infestations.

During childhood he had contracted the usual diseases. Tonsils and adenoids ..ere removed at the age of six years. He denied past allergic symptoms. During the war he had served on the islands of Guadalcanal (where he contracted malaria in 1942), Tulagi, Samoa, Tinian, Saipan, and Japan. He had spent a total of four years overseas in the Pacific area. His mother, father, sister, brother, and wife were all in good health, and there was no family history of allergy, tuberculosis, cancer or other familial diseases.

Physical examination upon admission to the hospital revealed a pale, asthenic, thin, 23 year old white male, appearing chronically ill. Temperature, pulse, and respiratory rate were normal. His height was 65 inches and he weighed 140 pounds. He coughed frequently. The facial skin showed pitted scars of former acne vulgaris. The body skin was rough and granular. The subcutaneous tissues were normal. The tonsils were surgically absent. The posterior cervical lymph nodes were small, discrete, firm and non-tender. This was also true of the submaxillary, right axillary, inguinal, saphenous and epitrochlear nodes. In the left axilla there were several large discrete, non-tender lymph nodes, each the size of a walnut. The trachea was in the midline, the chest symmetrical and fixed in a position of moderate inspiration. Upon auscultation, asthmatic rhonchi, sibilant and sonorous, were heard mainly during expiration. The chest was hyper-resonant, and tactile and vocal fremitus were normal. The heart rate was 88 per minute with a regular sinus rhythm. No thrills or murmurs were present and the heart was not enlarged. The abdomen was scaphoid, non-tender, and no masses were felt. The spleen was not palpable. The genitalia were normal adult male, and the extremities appeared normal. Chest roentgen-ray revealed moderate accentuation of both hilar and peribronchial markings but no parenchymal lesions. This was considered to be consistent with chronic bronchitis or bronchial asthma. Blood studies revealed 5,530,000 erythrocytes per cu. mm. with 15 gm. hemoglobin (107 per cent) and a leukocytosis of 28,950, 57 per cent of which were eosinophiles, with 15 per cent mature neutrophiles, 3 per cent monocytes, and 22 per cent lymphocytes. The eosinophiles were somewhat larger than those usually seen, with 2 per cent band forms and 98 per cent mature segmented forms. Examinations of stained sputum smears revealed numerous eosinophiles with a few neutrophiles, many Curschman's spirals, some elastic fibers and an apparently normal bacterial flora. No fungi, molds, or parasites were ever found in the sputum in spite of repeated examinations, and stained smears for acid-fast bacilli were invariably negative. Urinalyses were normal and the erythrocyte sedimentation rate (Westergren) was 6 mm. per 60 minutes. All stool specimens including those collected for 24 hours after purgation with magnesium sulfate were invariably negative for all ova and parasites. The Kahn test was negative.

During hospitalization the patient was free of dyspnea unless he lay down or exercised. After going to bed at night he noted the progression of wheezing, dyspnea and cough, particularly in the early morning hours. The cough was severe and productive of tenacious dark sputum, and paroxysms were usually followed by vomiting, so that he usually lost his breakfast. His symptoms were controlled with adrenalin and benadryl. However, his breathing during sleep was labored and audible throughout the ward. Roentgen-rays of the paranasal sinuses revealed some haziness of the frontal and maxillary sinuses bilaterally. Repeated chest roentgen-rays showed no change from the films made following admission. During the first week of hospitali-

zation he lost six additional pounds of weight. Temperature, pulse, and respiration remained normal. The white cell count increased to 17,750 with 61 per cent eosinophiles. An electrocardiogram made on February 17 revealed no evidence of myocardial damage, with normal sinus rhythm, rate 75 per minute, P–R interval 0.18 second, and T waves upright in all leads. The Davidsohn test was negative as were all routine febrile agglutination tests. Dark-field examinations of the blood serum were negative for parasites. Stool cultures were negative and sputum cultures on Sabouraud's medium showed no growth. The erythrocyte sedimentation rate was now 13 mm. in 60 minutes. On February 22 a large lymph node 25 mm. in diameter was removed from the left axilla. Upon microscopic examination, the lymph node architecture was well preserved. The capsule was thin and showed some blood vessel congestion. The follicles showed marked hyperplasia of the germinal centers with much lymphoblastic activity. The mature lymphocytes about the follicles were lined up in almost concentric rings. The peripheral sinuses were dilated and in some areas contained lymphocytes. Reticulo-histiocytic elements showed moderate hyperplasia, and an occasional large macrophage containing brown pigment granules could be seen. Large numbers of plasma cells and polys were present. No evidence of malignancy was noted and the histologic appearance of the node was consistent with the picture seen in tropical eosinophilia. Pathologically the histological diagnosis was chronic lymphadenitis with reticulo-endotheliosis.

The following skin tests were employed: (1) *Dipilidium caninum*, 0.5 c.c., intradermally, was positive, showing erythema, pseudopodia, and enlargement of the wheal to one-half inch within 15 minutes. The control remained negative. (2) *Trichinella spiralis*, 1:10,000, 0.02 c.c., intradermally was negative. (3) Coccidioidin, intradermally, gave positive results. (4) *Dirofilaria immitis*, 1:10,000, produced an immediate positive reaction in 30 minutes, the control remaining negative. (5) P.P.D. tuberculin test (first strength) was negative. (6) Skin tests for 36 common allergens, including air-borne pollens, foods, and animal dander were all negative.

On February 22 the erythrocyte sedimentation rate was 13 mm. in 60 minutes, hemoglobin 14.5 gm. (103 per cent), leukocytes 17,450, 49 per cent of which were eosinophiles. The platelet count was 378,000. Chest roentgenograms revealed some clearing of the hilar markings as compared with previous films. Roentgen-rays of the skull, long bones, and muscles were reported as negative for soft tissue calcifications which might represent encysted parasites. The patient now weighed 132 pounds. The basal metabolic rate was plus 13 per cent. The patient was treated with intramuscular adrenalin-in-oil and oral benadryl which gave some relief of his severe asthmatic symptoms. After seven days of this treatment a concurrent decrease in symptoms, leukocytosis and eosinophiles to 30 per cent occurred. This was probably coincidental.

Commencing on March 4, 100,000 Oxford units of penicillin were given intramuscularly every three hours to a total of 8,000,000 units. By the end of the course of penicillin, the eosinophilic count had increased slightly. The patient continued to gain weight and was free of symptoms. No changes were seen in the lung fields by weekly roentgen-rays.

Following the cessation of penicillin therapy, two weeks were allowed to elapse, but no significant change in the blood picture occurred, the leukocyte count remaining about the same and the eosinophiles ranging between 20 per cent and 30 per cent. Finally, on March 22 a course of six injections of neoarsphenamine intravenously was commenced. At first there was a steady decline in the eosinophilia from 30 per cent to 11 per cent, then it temporarily rose as high as 17 per cent, finally subsiding to within normal limits. The case could not be followed further, as the patient was discharged from the Service and returned to his home. When last seen in mid-April, he was gaining weight, symptom-free, and his blood counts were still normal.

Differential Diagnosis: The fact that this patient had served in the Pacific area throughout the war, including 11 months in Samoa where the *Wuchereria bancrofti* abounds, probably accounts for his illness which, however, did not become manifest until after he returned to the United States. The positive reaction to *Dirofilaria immitis* antigen, obtained through the courtesy of Dr. H. W. Brown of the Columbia University School of Public Health, is probably of significance as evidence of filariasis, although it is known that approximately 10 per cent false positives occur.[8] This antigen which is an extract of the dog heartworm has not, according to Huntington,[9] proved to be strictly specific for the filaria group since unmistakable cross-reactions with ascaris sometimes occur. Huntington further states that its value as a diagnostic aid in individual cases is decidedly limited.

No ova or parasites were ever found in the blood, urine, feces, lymph node biopsy, or sputum, although each was examined repeatedly. Those particularly sought for were *Strongyloides stercoralis, Schistosoma mansoni, Necator americanus, Ascaris lumbricoides,* and *Entameba histolytica.*

All agglutination tests were negative, including those for heterophile antibodies, brucellosis, typhoid-paratyphoid, tularemia, and typhus. A diagnosis of trichinosis was considered unlikely, although muscle biopsy was declined. The sputum was cultured for yeasts and fungi with negative results.

Loeffler's syndrome [10, 11, 12, 13] was considered. This disease is characterized by transitory pulmonary infiltrations, relatively high eosinophilia in blood and sputum and relatively mild, usually afebrile, clinical course. According to a recent editorial in the Journal of the American Medical Association [14] much remains to be learned about these transitory infiltrations in the lungs. The chest roentgen-ray findings in this case were not consistent with a diagnosis of Loeffler's syndrome. Periarteritis nodosa and intrinsic bronchial asthma were also considered, as well as eosinophilic leukemia and Hodgkin's disease. Finally, the therapeutic test gave convincing evidence that this was tropical eosinophilia as described by Weingarten.[1]

Discussion

Apley and Grant [6] in their excellent treatise pointed out the similarities between intrinsic asthma, periarteritis nodosa, Loeffler's syndrome, and tropical eosinophilia. These four diseases have many common features, including a chronic course, hypereosinophilia, asthmatic symptoms and signs, and no obvious etiology. They suggest that the difference between tropical eosinophilia and Loeffler's syndrome is more apparent than real, and that it would be profitable to consider them merely as different manifestations of the same disease process. They further suggest that this group of diseases be referred to as the "E–P" syndrome, meaning "eosinophilia with pulmonary disease."

That tropical eosinophilia can be cured by arsenicals leaves one to speculate concerning its etiology. The consensus is that it is an allergic response to a variety of allergens, including infestation with animal parasites such as mites, amebae, or filaria. However, an infestation with these parasites does not invariably produce the syndrome.

As has been shown repeatedly, the effect of arsenic in producing a complete recovery in tropical eosinophilia is remarkable but as far as we were able to determine, arsenicals have not been tried in the other three conditions, and penicil-

lin, in none of them. For this reason, we administered penicillin to this case, and as far as we could determine it had absolutely no effect.

The weight of evidence in regard to this group of diseases will doubtlessly continue to be that they are of an allergic nature. Rich [15, 16] has advanced the hypothesis that the lesions of periarteritis nodosa are the result of hypersensitivity, and in 1942 he reported five autopsies on patients who had serum sickness before death. In all of them he was able to demonstrate the characteristic lesions of periarteritis nodosa. He later demonstrated similar vascular lesions in two patients following reactions to sulfonamide therapy, and in the following year Rich and Gregory [17] succeeded in producing similar lesions experimentally in rabbits by sensitizing them to horse serum. This appears to be additional evidence in support of Apley and Grant's classification of these four diseases under the "E–P syndrome."

In regard to filariasis being a factor, whether allergic or infective, in tropical eosinophilia, it is known that after patients are removed from endemic areas they become symptom-free because the filaria are unable to multiply until they undergo further passage in mosquitoes, and hence die out. However, reliable therapeutic agents against filariasis are not known. The diagnosis is usually made without demonstrating the filaria and laboratory tests are seldom helpful.[18]

It is our opinion, unsupported by concrete evidence, but nevertheless in accordance with the conclusions of Van der Sar and Hartz, that this patient acquired a minimal infestation with *Wuchereria bancrofti* during his stay in Samoa. Following the death of the parasites upon his return to a temperate climate he developed the typical signs and symptoms of tropical eosinophilia. This failed to respond to treatment with penicillin but promptly subsided following the administration of neoarsphenamine.

Summary

A case is presented in which the clinical history, course and laboratory findings were consistent with a diagnosis of tropical eosinophilia.

The patient had been stationed in Samoa and gave a positive skin reaction to *Dirofilaria immitis*. This appears to be additive evidence to support the hypothesis of Van der Sar et al. and others, that tropical eosinophilia may be due to filarial infestation.

Penicillin is of no therapeutic value in this disease although the empirical use of organic arsenicals is amazingly effective.

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SULFADIAZINE NEPHROSIS WITH HYPERCHLOREMIA AND ENCEPHALOPATHY *

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Luetscher and Blackman have described a peculiar syndrome of hyperchloremia and encephalopathy, occurring in toxic nephrosis following sulfathiazole therapy.[1] The patients initially showed the usual critical oliguria or anuria, with azotemia, acidosis and a normal or low serum chloride level, which are typical of most acute toxic nephroses. The diuresis which followed this initial stage, however, was not the usual diuresis which is commonly welcomed as an indication that the patient will probably recover. On the contrary, despite a subsiding azotemia and acidosis, diuresis in these cases was accompanied by a striking elevation of the serum sodium and chloride levels. As this hypertonicity of the serum and body fluids increased, signs of dehydration and a severe encephalopathy appeared. The hyperchloremic encephalopathy may have been the major cause of death in at least two of the five cases reported, rather than the uremia or any other complication. In two cases treated with 3 to 5 liters of salt-free intravenous fluids daily, the serum chloride returned promptly to a normal level and the uremia continued to improve. The encephalopathy persisted, however, subsiding gradually over many months in one patient, but proving eventually fatal in the other case long after the uremia and hyperchloremia were controlled.

* Received for publication January 18, 1949.
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The primary renal defect responsible for hyperchloremia was clearly shown to be an inadequate tubular reabsorption of water in the face of continued electrolyte retention.[1] The serum bicarbonate level was not depressed, unlike the hyperchloremia found after administration of calcium chloride or other acid-producing salts.[2] Despite serum chloride levels of 140 to 160 milliequivalents per liter (normal 100 to 110), the urine, though always of considerable volume in the hyperchloremic stage, showed a very low fixed chloride concentration. Similarly, in one patient it was shown that 97 per cent of the chloride in the glomerular filtrate was reabsorbed by the tubules, while only 90 per cent of the water was reabsorbed. Glomerular filtration was 30 per cent of the expected normal rate.

Autopsied cases showed a severe toxic tubular nephrosis with necrosis and thrombosis of adjacent interlobular veins and minimal glomerular damage. The brains examined showed widely scattered foci of gliosis, edema and hemorrhage.

The extreme degree of hyperchloremia without acidosis was considered to be clinically almost unique among renal disease and among other causes of electrolyte disturbance. A comparable hyperchloremia, however, has been produced experimentally in dogs by Winkler and his co-workers.[3, 4] By injecting hypertonic saline solution they produced chloride levels up to 193 milliequivalents per liter and found a generalized intracellular dehydration as well as a loss in intracellular potassium. The cerebral type of death in these dogs, without cardiorenal failure, was somewhat reminiscent of Luetscher's cases of hyperchloremia in man. There was no evidence for the existence of a critical level of either sodium or chloride in dogs.

Even since the original report of hyperchloremia in sulfathiazole nephrosis, the syndrome has not been widely recognized or reported.* It therefore seemed worthwhile to report a case which followed the oral administration of small doses of sulfadiazine.

Case Report

A 23 year old single unemployed Italian man entered the Peter Bent Brigham Hospital on Dec. 14, 1945, in coma.

At the age of seven he developed chronic osteomyelitis of the right femur, treated by open drainage, with fractures of the same bone and recurrence of the infection at 10 and 13 years of age. At 10 years of age he also had pyelitis. Up to the age of 17, he was crippled by an increasing shortening and bowing of this leg, requiring a lift and brace. At the age of 17, six years before the present illness, he had had a supracondylar osteotomy at the Massachusetts General Hospital to correct the deformity. Sulfanilamide was given prophylactically, 3 to 6 gm. daily for six days. Nine days postoperatively a staphylococcus infection recurred at the operative site requiring two courses of seven days each of sulfanilamide, 5 to 6 gm. daily, and three days of sulfapyridine, 4 gm. daily. Urine, white blood count and hemoglobin remained normal throughout the three month hospital course without drug fever or rash.

Recovery followed without further recurrence and he was left with only a slight limp from a one inch shortening. As a devotee of boxing and a professional sparring partner, he received frequent blows to the head but no known concussion. He was considered by his family physician to be an inadequate person, never able to hold a

* Maisel, Kubik and Ayer [5] reported a case of encephalopathy following sulfathiazole therapy with an elevated non-protein nitrogen which fell to normal terminally, without progressive oliguria, and yet with a progressively fatal coma. At autopsy, both renal and cerebral lesions were found, quite similar to those reported by Luetscher and Blackman. Clinically and pathologically the resemblance was close enough to suggest that the hyperchloremic syndrome may have been present, although no serum chloride determination was reported.

steady job, blaming his incapabilities on his former deformity, occasionally showing extremely introspective as well as paranoid behavior. He would often threaten people unaccountably, occasionally quite violently, and in the few months preceding admission he became increasingly nervous and moody.

Three weeks before admission he developed malaise, low back pain and after several days a headache, chilly sensations and a fever up to 103 degrees. The urine showed no albumin or sugar; the sediment was not examined. Physical examination was negative. He was given 1 gm. of sulfadiazine and 2 gm. of sodium bicarbonate orally every three hours for a total of only four doses. On the second day his temperature was normal and he was up and about the house. On the third day he complained of a headache and suddenly became very moody, finally quite violently paranoid, threatening his family with a carving knife for no apparent reason and attempting to strangle a neighbor.

He was accordingly first admitted to the Boston Psychopathic Hospital where he was found to be combative, confused, acutely maniacal, and so violent that he had to be kept in padded isolation. Physical examination was essentially negative. For the first seven days in the Psychopathic Hospital observations were necessarily limited by his extreme violence. His appetite and fluid intake were fair. Urination was noted to be very scanty, but it was uncontrolled and not measured. On the first day lumbar puncture under pentothal anesthesia showed normal dynamics, 15 lymphocytes per cubic millimeter, a positive Pandy test, and a total protein of 25 mg. per cent; lumbar puncture repeated six days later showed a total protein of 95 mg. per cent. On the sixth day the blood serum non-protein nitrogen was 94 mg. per cent, rising to 200 by the twelfth day. Initial urine specimen on the twelfth day showed occasional red and white blood cells, granular casts and a 1 + albumin.

By the second week of his Psychopathic Hospital stay, he had become less violent and fairly coöperative, taking fluids well and urinating copiously, although still incontinent. From the tenth to the thirteenth day, however, he became increasingly stuporous and his total output had meanwhile risen to over 1,000 c.c. On the eleventh and twelfth days 4,000 c.c. of parenteral fluids, containing a total of only 9 gm. of sodium chloride and 3 gm. of sodium bicarbonate, were given daily and the urine output rose to almost 2,000 c.c. On the thirteenth day the non-protein nitrogen had fallen to 171 mg. per cent but the serum chloride was found to be elevated to 146 milliequivalents per liter. He was now comatose and totally incontinent.

It was decided on consultation to transfer the patient to the Peter Bent Brigham Hospital. On admission to this hospital, the rectal temperature was 101.2°, the pulse 98 and the respirations 20. The patient was a well developed, slightly obese young man who was comatose except for occasional mumbling and singing to himself. The skin was hot and dry without detectable edema. The subcutaneous tissue and muscles were firm, without signs of wasting or weight loss. A diffuse, thinly scattered, fine maculopapular rash covered the chest and back, with several small macules over the face. The right leg showed the old osteotomy scar and was one inch shorter and definitely smaller than the left. The right knee was limited to 70 degrees of flexion. The conjunctivae were suffused. The pupils were dilated and reacted slowly to light. The fundi were normal. The nasal mucosa was congested and there was a yellow mucoid exudate obstructing the nares. The breath was foul and uriniferous. The lips and tongue were extremely dry and crusted. The neck was not stiff. The chest was repeatedly clear to percussion and auscultation. The heart was not enlarged and showed a normal sinus rhythm with no murmurs or friction rubs. The abdomen, genitalia and rectum were normal. The deep tendon reflexes were hypoactive but present throughout and there was no Babinski sign.

Laboratory Data: Hinton negative. Urine: pH 5.5, specific gravity 1.008, albumin 2 + with occasional red cells, 1 to 3 white cells and 1 to 3 granular casts per

high power field in the unspun sediment. Urine guaiac positive, stool guaiac negative. Hematocrit 51.5 per cent, hemoglobin 17.2 gm. per cent, corrected sedimentation rate 0.9 mm. per minute, white blood cell count 6,700 with 66 per cent polymorphonuclears, 14 per cent band forms, 16 per cent lymphocytes and 4 per cent eosinophiles. Blood urea nitrogen 104 mg. per cent, serum non-protein nitrogen 170 mg. per cent, total protein 8.4 mg. per cent, fasting blood sugar 65 mg. per cent, serum carbon dioxide combining power 22 millimoles per liter, serum chloride 140 milliequivalents per liter, icteric index 15, sulfadiazine level 0. Electrocardiograms and skull films were normal. A chest film was normal except for prominence of the left ventricle. Two blood cultures and a urine culture were negative.

Hospital Course: An intake of over 4,000 c.c. of salt-free intravenous glucose lowered the chloride level from 140 to 113 milliequivalents per liter and the hematocrit from 51.5 to 43 per cent within the first 36 hours. The high fluid intake was continued, however, for an additional 12 hours until the report on the rapid fall in serum chloride had been received and evaluated. By 48 hours after admission the patient had received a total of 7,000 c.c. of salt-free fluids, dehydration had disappeared, a gain in weight of 3 kg. was noted, and he looked slightly edematous. Fluid therapy was therefore suspended. A few hours later his temperature suddenly rose to 105 degrees, the pulse to 144 and the respirations to 60, and the latter were deep as well as rapid. Emergency chemical determinations showed a rise in the blood urea nitrogen to 140 mg. per cent and a fall in the serum carbon dioxide combining power to 18.9 millimoles per liter. He was given 80 c.c. of a one molar sodium lactate solution and 20 gm. of salt-free albumin in 1,000 c.c. of dextrose and water. The temperature then promptly fell to 101.6°, the pulse to 100, the respirations to 40, and the serum carbon dioxide combining power rose to 21.9 millimoles per liter within a few hours. On the third day oliguria progressed gradually to a state of anuria so that intravenous fluid therapy was again suspended. Generalized edema was now obvious with pitting in the sacral region. Finally, the blood pressure fell below 100 mm. of mercury and the respirations became very shallow while the temperature rose again to 105°. There were no signs of pulmonary edema at any time, however, and an electrocardiogram and repeated examinations of the heart at this point were normal. Despite 4 units of plasma and the usual stimulants, he died 78 hours after admission, in shock, with a terminal hyperpyrexia of 108.2 degrees.

Autopsy: The body was that of a normally developed and well nourished white man. There was a moderate degree of pitting of the lower extremities and sacral region. The heart was not remarkable. In the lungs, large irregular areas of consolidation, proved by microscopic examination to be confluent bronchopneumonia, were found scattered throughout all the lobes. The liver appeared normal. The right kidney weighed 260 gm. and the left kidney 350 gm. They were of the usual shape. The arrangement of the ureters and renal vessels at the pelvis was normal. The renal capsules were thin and could be stripped with ease leaving smooth, firm, pale reddish-brown surfaces. Vertical sections of each kidney showed the cortex and medulla to be clearly demarcated. The cortex of each kidney measured from 1.0 to 1.2 cm. in width. The tubular striations of the papillae were clearly seen. The cut surfaces appeared edematous and moist and the cortex protruded above the capsule. The calyces and pelves and ureters were normal in shape and thickness. Numerous pinpoint hemorrhages were found in the pelvis and papillae. No significant gross findings were noted in any of the other organs. Permission for examination of the brain was not granted.

Microscopic Studies: Sections of kidney were fixed in Zenker's fluid and in 10 per cent formalin and stained with eosin-methylene blue, hematoxylin-eosin, Kossa's silver stain for calcium, Turnbull's blue stain for iron, and benzidine stains. The most striking renal lesions involved the tubules. Many tubules were dilated and the

lining epithelium was flattened. In others the epithelium was thin, atrophic and fragmented. Many epithelial cells were separated from the basement membranes. Other tubular areas showed definite evidence of repair with binucleated cells and mitotic figures. Three types of casts were found in the tubules (figure 1). The most prominent were large, irregular refractile masses which stained a deep blue-black with the eosin-methylene blue stain. The appearance of the material suggested calcium.

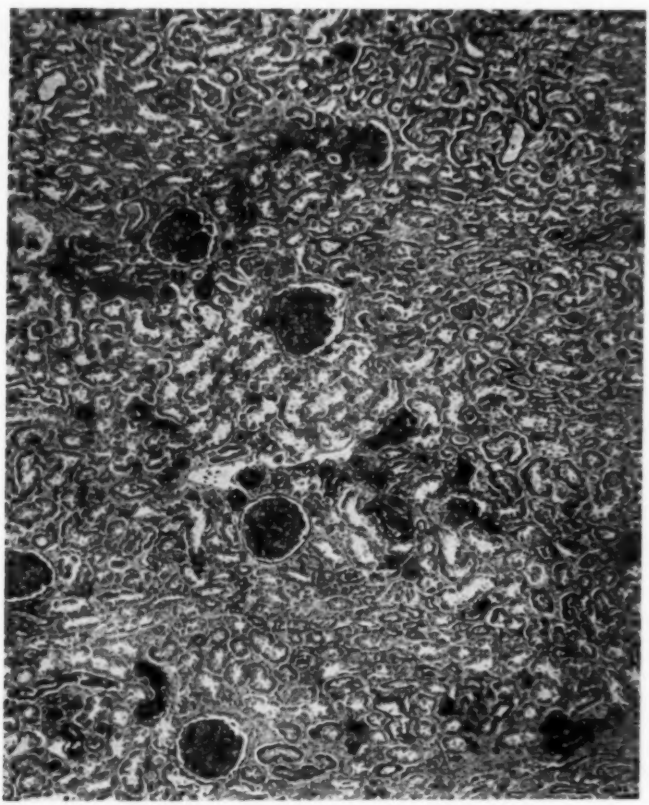

FIG. 1. Low power photomicrograph illustrating the large numbers of casts present in the tubules. Eosin-methylene blue stain.

These casts completely filled the lumina of the tubules. The lining epithelium was always disrupted to a greater or lesser degree and the epithelial cells were either swollen or fragmented (figure 2). This material did not give positive reactions to either the iron or benzidine stains. This was true as well for Kossa's silver stain for calcium phosphate. However, when sections of kidney tissue were subjected to micro-incineration these casts reacted positively to tests for calcium and to a lesser

degree for iron. These casts were present for the most part in the intercalated segments of the distal convoluted tubules, but were occasionally found in the loops of Henle and in the proximal portion of the collecting tubules. The next type of cast in order of frequency was a pale, slightly basophilic, homogeneous cast and these casts were interpreted as being made up of protein. These casts did not react with the iron, benzidine or Kossa's silver stain for calcium. The third type of cast was

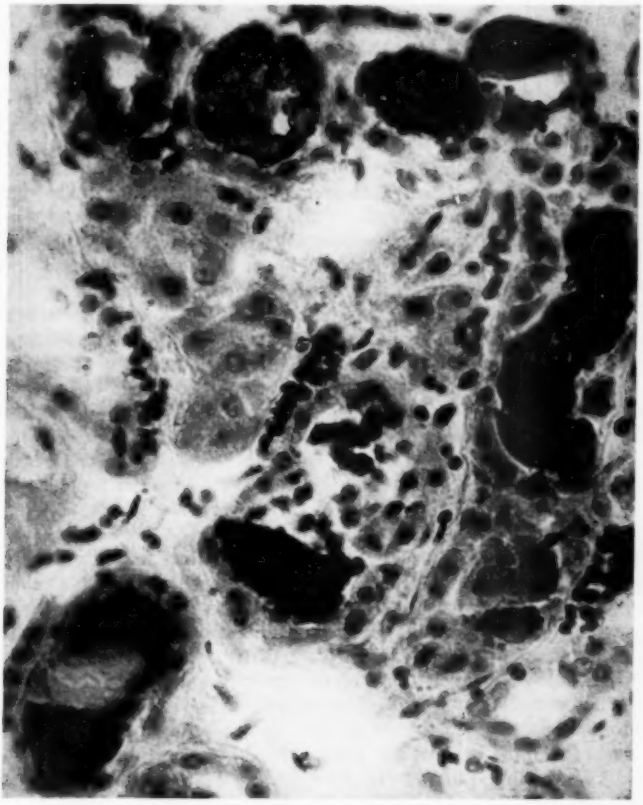

FIG. 2. High power photomicrograph showing the character of the refractile tubular casts. Eosin-methylene blue stain.

made up of finely granular material which stained reddish-brown with the eosin-methylene blue stain. This material had the appearance of hemosiderin and this was confirmed by the iron stains.

It should be noted that in addition to the above findings small collections of reddish-brown pigment suggesting hemosiderin and giving a positive reaction to the iron stains were found in the epithelium of some of the tubules.

The glomeruli were not unusual in any way. The large and small blood vessels were negative.

Bacteriology: Staphylococcus aureus was cultured from the lungs; *B. coli*, enterococci, and a rare *Staphylococcus aureus* were cultured from the right kidney pelvis; and *B. coli* from the pelvis of the left kidney.

Discussion

The clinical course and pathological findings in the case presented compare closely with those reported by Luetscher and Blackman [1] and serve mainly to establish the existence of the hyperchloremic syndrome following sulfadiazine, as well as following sulfathiazole as originally reported. The initial oliguria, followed by hyperchloremia, dehydration and coma appearing in the face of a diuresis, and the hyperpnea without acidosis were all similar to their findings. Clinically, however, it is impossible to say how much of the patient's encephalopathy was due to hyperchloremia, to uremia or to direct sulfonamide toxicity.[5-9] In addition, the patient's known background of paranoid and schizoid tendencies may have influenced the initial symptomatology which prompted his admission to a psychopathic hospital, for it is well known that organic disease, including both uremia and sulfonamide intoxication,[6, 10] may bring out a latent psychosis.

The extensive tubular damage, the type of casts found in the tubules and the minimal evidence of glomerular damage were similar to the renal lesisons originally reported. On the other hand, thrombosis and necrosis of the interlobular veins were not found in this case, nor was there any evidence of vascular damage either in the kidneys or elsewhere in the body. The tubular lesions were more diffuse than in the cases of Luetscher and Blackman. The peculiar association of excessive tubular loss of water with continued electrolyte retention was felt by these authors to be due to a specifically localized tubular lesion. Actually, however, the lesions described in their cases were also fairly well scattered throughout the tubular system.

Therapy: Salt-free intravenous fluids, using up to 4 to 5 liters daily, were used by Luetscher and Blackman specifically to offset the excessive tubular loss of water and thus to lower the serum sodium and chloride to isotonic levels. Salt, or sodium in any form, is obviously strictly contraindicated in hyperchloremia. The apparently irreversible nature of hyperchloremic encephalopathy [1] suggests that such treatment must be prompt and vigorous, preferably started following discovery of an elevated serum chloride and before cerebral damage from hyperchloremia becomes obvious clinically. However, pulmonary edema may be a limiting factor in the intravenous administration of even small amounts of salt-free fluids, as was found in two of Luetscher's cases, and in such a situation attempts should be made to use the less effective subcutaneous or oral route of administration.

Generalized edema may also occur following the excessive use of even salt-free fluids as illustrated by the present case. The serum chloride level was lowered rapidly, and the parallel fall in hematocrit suggests that therapy produced a simple dilution of the blood and probably the remainder of the body fluids as well. The high fluid intake was mistakenly continued, however, for at least 12 hours after relief of the hyperchloremia. Meanwhile, the urine output was again falling possibly representing a change in the functional state of the kidneys as they

approached a terminal stage of the disease. With increasing oliguria, excessive fluids given once dehydration had been corrected could only have tended to form edema fluid. Generalized edema appeared in this case despite the fact that fluids administered contained no salt and despite the probability that the total body electrolyte content was never increased.* This edema, by including the kidney as found at autopsy, may have contributed to the eventual total renal failure. In the brain, edema may have aggravated the encephalopathy as suggested by the terminal hyperpyrexia of 108.2°.

A high salt-free fluid intake is therefore probably indicated only while hyperchloremia is actually present. Once hyperchloremic dehydration is controlled the fluid intake should depend upon the urine output. It has been repeatedly emphasized that in the usual toxic nephrosis without hyperchloremia, a high fluid intake will not force an oliguric or anuric kidney to increase its urine output and will only tend to add the further complication of pulmonary or generalized edema.[12, 13]

Finally, generalized depletion of intracellular potassium may well be an important pathophysiological factor in these cases, as found by Elkinton, Winkler et al. in dogs.[3, 4] The possible benefit of potassium replacement therapy should be emphasized.

Alkalization in Sulfonamide Therapy: In preventing renal damage from sulfonamides, the value of routine adjuvant alkali therapy is debatable. The various renal lesions to be considered are outlined in table 1. Of these lesions, only Group I, the crystallurias, are preventable by the use of alkali. Sulfonamides and their esters are relatively insoluble in an acid urine and the crystals can cause irritation, hematuria and obstruction at any point from the tubules to the bladder. Sodium bicarbonate, or sodium r-lactate, given in sufficient dosage of 12 to 22 gm. daily has been shown to decrease or eliminate crystalluria by raising the pH of the urine to at least 7.5 at which point the sulfonamides are quite soluble.[13-15] However, even obstructive anuria with uremia, the most serious complication of crystalluria, may be readily treated by ureteral lavage or nephrostomy, usually with complete recovery.[11] An adequate fluid intake and avoidance of overdosage by determinations of the blood sulfonamide level will also help greatly to prevent these reactions.

The more serious sulfonamide nephropathies, toxic nephrosis [16-19] and those due to hypersensitivity,[20-22] often lead to irreversible renal damage if not a direct fatality (table 1, Groups II and III). These lesions are apparently unrelated to crystalluria, however, and their incidence is not decreased by the use of alkali, judging from a review of the larger series of experimental and clinical studies.[16-19, 22-26] On the contrary, Earle has shown that sodium bicarbonate greatly increases the tubular excretion of sulfamerazine, lowering the blood level so that a higher dosage is required and thus increasing the total exposure of the tubular cells to this toxic agent.[27]

* Patients with renal disease show a pathological tendency to divert salt and fluid from the blood into the tissues even with a body electrolyte content which is usually normal or low. For example, most nephritics are unable to develop the transient hydremia of approximately 4 per cent which is seen in normals after the ingestion of hypertonic saline solution.[10] Such salt solutions are taken up almost immediately by the tissues to form edema fluid in the nephritic, without even a transiently detectable hydremia. This fact might explain why even salt-free fluids greatly in excess of the urine output could alone carry a patient with renal insufficiency from a state of hyperchloremic dehydration over to one of generalized edema at a normal or low serum chloride level.

TABLE I

Renal Lesions Due to Sulfonamide Drugs

I. *Crystalluria* (obstructive and irritative, due to deposits of drug insoluble in an acid urine)
  A. *Extranephric* (calyces, pelves, ureters, bladder) [29-30]
    Persistent renal calculi [31]
    Radio-opaque membranous pyelitis [32]
  B. Intranephric (tubules and rarely glomeruli) [16, 19]
II. *Toxic Nephrosis* (focal or diffuse tubular damage without demonstrable crystalline deposits)
  A. Nephrosis with uremia, oliguria, and normal or low chlorides [16-19]
  B. Nephrosis with uremia, hyperchloremia and encephalopathy (Luetscher and Blackman [1])
  Associated lesions:
  1. Glomerular damage (rare) [1, 19]
  2. Thrombosis of adjacent interlobular veins [1, 5, 17] (see IIIB) *
III. *Lesions of Hypersensitivity* (disseminated focal lesions in the kidneys and other organs)
  A. Periarteritis nodosa [20-22]
  B. Focal thrombophlebitis,* renal interlobular and splenic trabecular veins [1, 5]
  C. Focal disseminated interstitial necrosis
    1. Miliary granulomata [6, 17, 19, 33]
    2. Acute miliary aseptic necrosis [34-36]

(Combinations of many of the above lesions have been reported)

* Luetscher and Blackman [1] felt that focal thrombophlebitis was due to contact of the damaged tubule and irritative drug with the wall of an adjacent vein, while Maisel, Kubik and Ayer [6] considered it to be a part of a more generalized sensitivity reaction.

Alkalization of the urine, therefore, is probably of questionable value except in preventing the relatively innocuous renal sulfonamide reactions which involve crystalluria, and then only when given in a very high sustained dosage. A proper selection of cases for sulfonamide therapy, an adequate fluid intake and a proper regulation of dosage by determinations of the blood sulfonamide level are the obvious precautions which should help most to lower the incidence of serious or fatal sulfonamide nephropathies.

SUMMARY

A fatal case of toxic nephrosis following the administration of only 4 gm. of oral sulfadiazine, associated with hyperchloremia and encephalopathy, has been presented. The rapid exitus with a cerebral type of hyperpyrexia and shock, without evidence of cardiac failure or pulmonary edema, suggests that the encephalopathy may have been a major cause of death. A direct relationship between encephalopathy and hyperchloremia per se, however, cannot be proved in this case. Early diagnosis of hyperchloremia by frequent determinations of the serum chloride level is important in such cases of acute renal disease before irreversible changes from intracellular dehydration can occur. Since the mechanism of hyperchloremia consists of a selective water diuresis with continued sodium and chloride retention, it is not encountered during the initial stage of anuria in toxic nephrosis but rather during the diuresis of recovery. During the hyperchloremic syndrome a subsiding azotemia, minimal acidosis and a moderate or large urine volume with a very low fixed concentration of sodium and chloride may be found.

Specific therapy includes the maximum amount of salt-free fluids which can be tolerated without the appearance of pulmonary or generalized edema, usually 3 to 5 liters daily, preferably intravenously. As soon as the hyperchloremic de-

hydration has been controlled the volume of fluid intake should usually be promptly restricted, depending upon the urine output, in order to avoid overtreatment to the point of causing generalized edema.

Potassium replacement therapy may well be indicated, judging from the evidence of generalized intracellular potassium deficiency in experimental hyperchloremia in dogs.

This case once more illustrates the potential dangers of sulfonamide therapy, even in small oral doses, and the ineffectiveness of routine alkali administration in preventing a fatal sulfonamide nephrosis.

Addendum

Since this report was completed, two additional cases of hyperchloremia and hypernatremia without marked acidosis, have been observed at the Peter Bent Brigham Hospital. Both cases showed a toxic encephalopathy. One followed the use of sulfathiazole, and was also referred from a psychopathic hospital, having shown initially a predominance of psychotic symptoms. The other case occurred following severe gastrointestinal hemorrhage, and will be reported in detail by Merrill and his associates, among a series of patients treated by means of a modified Kolff artificial kidney.[37]

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EDITORIAL

AMINOPTERIN IN THE TREATMENT OF ACUTE LEUKEMIA

THE inhibition of the biological activity of an essential metabolite by compounds which are structurally related to it is now a well known phenomenon. The underlying principles believed to be involved and their importance in the study of fundamental metabolic processes have previously been discussed in this journal.[1] Folic acid (pteroyl glutamic acid) and its specific antagonists constitute one of the most carefully studied examples of this relationship. By an antagonist in this sense is meant a substance which will inhibit the growth of *Lactobacillus casei* in a suitable culture medium containing barely adequate amounts of folic acid, but whose inhibitory action can be overcome by adding more folic acid to the medium. Within appropriate quantitative limits, a similar antagonism can be demonstrated in experimental animals.

Stimulated by the observations of Lewisohn and associates that *L. casei* fermentation factor (containing pteroyltriglutamic acid) frequently caused regression of certain breast cancers in mice, Farber et al.[2] administered this material to human subjects with various types of inoperable malignant tumors. In certain cases it seemed to be beneficial in causing subjective improvement and diminution in size of the tumor. When given to cases of acute leukemia, however, it seemed to accelerate and aggravate the process. This led them to try the effect of folic acid antagonists, and in 1948 [3] they reported obtaining temporary remissions in 10 of 16 cases of acute leukemia. These observations aroused widespread interest, and folic acid antagonists have been employed on an experimental basis in the treatment of acute leukemia in many clinics. Several different compounds have been used with more or less effect, but at present the most potent and most extensively employed is aminopterin (4-aminopteroyl glutamic acid).

Farber [4] has since summarized the results obtained by his group. Of about 60 children treated for three weeks or longer, somewhat over 50 per cent showed clinical or hematological improvement or both. Reports of other observers have in general confirmed Farber's observations that remissions may be obtained, but the frequency of such remissions has varied greatly in different clinics.

Dameshek and his associates [5] have studied a series of 34 cases, chiefly

[1] SACKS, M. S.: Biologic competition between structurally related compounds, Editorial, Ann. Int. Med., 1949, xxx, 867–870.

[2] FARBER, S., et al.: The action of pteroyl glutamic conjugates on man, Science, 1947, cvi, 619–621.

[3] FARBER, S., et al.: Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl glutamic acid (aminopterin), New England Med. Jr., 1948, ccxxxviii, 787–793.

[4] FARBER, S.: Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer, Blood, 1949, iv, 160–167.

[5] DAMESHEK, W.: The use of folic acid antagonists in the treatment of acute and subacute leukemia, Blood, 1949, iv, 168–171.

in adults. Of these eight died within five days and were virtually untreated. Of the 26 surviving for a longer period, nine or 34 per cent had remissions. Wolman et al.[6] reported remissions in seven of eight cases of acute leukemia. More recently Stickney et al.[7] from the Mayo Clinic observed complete remissions lasting up to four months in five of 21 children and in three of 33 adults. Partial remissions were obtained in eight additional cases (five children and three adults).

On the other hand Conley [8] obtained no remissions in nine cases of acute leukemia so treated. In seven cases there was a fall in the total leukocyte count, but abnormal cells did not disappear from the blood, the marrow continued to show a leukemic pattern, and there was no striking clinical improvement. The results in a larger series of cases subsequently treated have not been materially different.[9] Meyer et al.[10] obtained clinical and hematological improvement in only four of 43 cases. In 15 cases treatment was stopped because of severe toxic effects of the drug, and 24 cases were not materially affected.

The reason for such divergent results is not evident. The criteria of a remission employed by various observers may differ. It is questionable whether the failure to obtain remissions is due merely to inadequate dosage, since toxic reactions were common in these series. However, the margin between an effective dose and a dangerously toxic dose is at times very narrow, and the more successful observers may have continued treatment with greater hardihood in spite of alarming toxic symptoms.

In cases obtaining a satisfactory remission there have been marked subjective improvement, subsidence of fever and bleeding and an increase in strength so that within two or three weeks certain patients have been able to resume normal activities. There is a reduction in the total leukocyte count to normal or even to leukopenic levels. The primitive cells diminish in number or may disappear from the blood, so that it appears normal. The bone marrow tends to revert toward a normal pattern with a marked diminution in the percentage of blast cells. Some have reported that films of the marrow became normal, whereas others found some abnormality persisting. There may be an erythrocytic hyperplasia with the appearance of megaloblasts in the marrow, as might be expected with a deficiency of folic acid. With this there may be a rise in the red cell count and an increase in blood platelets. There may be a diminution in the size of the lymph nodes and spleen which is sometimes very marked.

Such remissions may last for a few weeks or months, but as a rule aminopterin must be continued in a reduced maintenance dose or a relapse

[6] Wolman, I. J., et al.: Leukemia in childhood. Preliminary report of response to aminopterin, Pennsylvania Med. Jr., 1949, lii, 474–481.

[7] Stickney, J. M., et al.: The treatment of acute leukemia with folic acid antagonists, Proc. Staff Meet., Mayo Clin., 1949, xxiv, 525–533.

[8] Conley, C. L.: Aminopterin in the treatment of acute leukemia (abstract), Bull. Johns Hopkins Hosp., 1949, lxxxiv, 395.

[9] Personal communication.

[10] Meyer, L. M., et al.: Aminopterin (a folic acid antagonist) in the treatment of leukemia, Am. Jr. Clin. Path., 1949, xix, 119–126.

quickly follows. If a relapse occurs, resumption of a full dose may bring about further remissions. Patients have been maintained in reasonably good condition in this way for many months, and one case for nearly two years. Eventually, however, either they fail to respond to aminopterin or grave toxic symptoms necessitate terminating treatment, the disease progresses, and death ensues. No case has been cured. Aminopterin seems to be ineffective in chronic myeloid leukemia.[7, 11]

Aminopterin is a potent and very dangerous drug, and its effects are by no means limited to the hemopoietic tissues. Toxic manifestations are frequent and often severe. In many cases they are unavoidable if an effective dose is administered. One of the commonest is an ulcerative stomatitis which is often but not invariably associated with a leukopenia. Manifestations of a gastroenteritis are also frequent. More serious are profuse hemorrhages, especially from the nose and gastrointestinal tract, which may be uncontrollable. Leukopenia is common, and there may be an extreme granulocytopenia with increasing anemia and thrombocytopenia, associated with hypoplasia of the marrow which may be irreversible. Cutaneous eruptions have been described in severe cases. Among occasional minor manifestations may be mentioned alopecia and deafness.

Ulcerations of the buccal mucous membranes and hemorrhages are common manifestations of the disease and do not necessarily contraindicate treatment with aminopterin. In patients who are under treatment, however, it may be difficult to determine whether such symptoms are referable to the disease or to the drug.

Individual susceptibility to aminopterin varies, and the dose has to be adjusted for each case. Severe toxemia may appear abruptly. It often subsides, however, if aminopterin is stopped promptly and suitable treatment administered (folic acid, transfusion, antibiotics).

There are obvious difficulties in interpreting the results of treatment in these cases. Spontaneous remissions occur occasionally in acute leukemia. The frequency with which they occur is not known precisely, but Diamond's [4] estimate of 10 per cent is probably a maximum figure. Furthermore spontaneous remissions as complete and long lasting as those described in some of the reported cases are quite rare. There can be little doubt that aminopterin has favorably influenced the course of the disease and that its effect is much more definite than that of the other procedures which have been previously employed.

It is equally evident, however, that aminopterin is a highly unsatisfactory therapeutic agent. Its action is unpredictable, and it is effective in only a minority of the cases. Its effect is temporary only, and no cure, nothing more than a transient remission can be hoped for. It causes serious toxic reactions, and some degree of such action must be anticipated if effective quantities are given. In many cases these reactions are prohibitively severe.

[11] BERMAN, L., et al.: Use of a folic acid antagonist in chronic leukemia, Am. Jr. Clin. Path., 1949, xix, 127–133.

For the present, the use of aminopterin is still experimental and should properly be restricted to clinics in which the patients can be observed with great care and corrective measures instituted promptly if serious toxemia develops. Under such conditions aminopterin may justifiably be employed since it offers a reasonable prospect of prolonging life and increasing comfort in some cases.

The chief importance of this work is that it opens up a new field for investigation of the treatment of neoplastic diseases. Even if no more satisfactory antagonist to folic acid should be found, there are many other essential metabolic processes in the cells which might be influenced in a similar manner if the chemical reactions involved were precisely known. The hope is justified that some substance may be found which would act more specifically upon the metabolism of neoplastic cells and presumably be more effective and less damaging to other tissues.

P. W. C.

REVIEWS

Conditioned Reflexes and Neuron Organization. By JERZY KONORSKI. 267 pages; 14.5 × 22.5 cm. Cambridge University Press, London; Macmillan Co., New York. 1948. Price, $4.00.

This book is written by a former pupil of Pavlov's working in Poland, whose laboratory was destroyed and whose researches were interrupted by the war. The intention of the author is shown by his dedication to Pavlov and Sherrington: ". . . In the hope that this work will do something to bridge the gulf between their respective achievements."

It is not a book for the amateur or general reader, but is only for those who are already deeply steeped in either Pavlovian tradition or neurophysiological work.

The author takes up in detail the basic concepts of Pavlov which he considers need thorough revision, for example internal inhibition, irradiation, induction, summation, sleep, nomenclature. He feels that the material contributed by Pavlov is of enormous importance, not only in its special field but for the advancement of more strictly neurophysiological research. He claims that his concept of higher nervous activity is in harmony with general physiology of the nervous system and the neuronic theory. The elaboration of a conditional reflex he thinks depends upon new functional connections in the brain and the multiplication of synapses. Unless there is repetition of excitation within a certain period the synaptic connections undergo atrophy. Internal inhibition consists in a formation of used synaptic connections of inhibitory character. The author feels that in spite of the erroneous nature of some of Pavlov's theories, the great physiologist has enormously enriched our knowledge of the nervous system and the ability to explore its intricacies in the future through the method of study of the conditional reflex.

W. HORSLEY GANTT

Modern Practice in Psychological Medicine. Edited by J. R. REES, M.D. 488 pages; 17 × 25 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper and Bros., New York. 1949. Price, $10.00.

This book is a collection of papers by a group of outstanding British and Canadian psychiatrists and psychologists. The topics covered are chapter headings of what one would expect in a textbook of psychiatry. As one can expect, there is some unevenness of excellence and considerable overlapping of topics. On the whole, however, the book is timely, up-to-date and of value as a general introduction to physicians who wish to know more about the emotional aspects of their patients. The point of view on the whole is conservative and practical. The editor, Dr. J. R. Rees, writes a chapter on Psychotherapy which is full of sound and useful advice to the general practitioner.

H. W. N.

Heart: A Physiologic and Clinical Study of Cardiovascular Diseases. By ALDO A. LUISADA, M.D. 653 pages; 25.5 × 19 cm. The Williams and Wilkins Company, Baltimore. 1948. Price, $10.00.

The simple but comprehensive title of this book is well chosen, for its contents are not confined to *diseases* of the heart. With a background of over 20 years of investigative and clinical cardiology, the author has a unique and intimate knowledge with which to endow his work, and a wealth of cardiac physiology is included. There

are probably no other 600 consecutive pages in print which contain so much and so diversified cardiological information.

While no aspect of the heart is overlooked, there is an admitted emphasis on "mechanized" cardiology. Thus in the description of each disorder, besides the expected discussion on electrocardiographic and radiological findings, there is an account of the changes to be found in cardiogram, pneumocardiogram, electrokymogram, arterial and venous pulse tracings, and, most particularly, in phonocardiogram.

Among the outstanding merits of this book is the exceptionally large number of excellent illustrations, especially those which present, in one form or another, graphic registrations of cardiac action. Another good point is the inclusive bibliography which covers both American and European literature. A minor criticism is that many of the illustrations would be even more valuable with fuller descriptive legends; similarly in the text, which is necessarily condensed, the author sometimes achieves brevity at the expense of clarity.

Dr. Luisada clearly has a passion for eponymy. For example, the chapter on pericardial diseases contains no less than thirty such designations, and the text in general is peppered with eponyms—from Auenbrugger's sign to Zeri's syndrome. This is a mere observation of interesting fact and is not intended to imply any criticism whatever. The preservation of historic names has much to be said for it.

Whether or not the author subscribes to its use, it is surprising to find no mention of Dicumarol in the treatment of myocardial infarction. Dr. Luisada has kept the expression of personal views within moderate limits; he gives his own explanations, however, for several circulatory phenomena, such as some of the signs of aortic insufficiency. And such views, held as they are by an exceptionally thorough investigator, must command respect and stimulate enquiry, even if they are not given ready acceptance. The author has also deviated from the "orthodox" *etiological* classification of heart disease, because he believes that this "scheme of beautiful simplicity" encourages a mental laziness in formulating exact diagnoses. Instead he has adopted a classification based on anatomical-clinical syndromes.

This book has been written "for the large group of physicians who desire to increase their knowledge of heart disease." There must be few cardiologists, and fewer internists, whose knowledge of cardiovascular physiology and pathology will not be substantially increased by a careful perusal of this informative book.

H. J. L. M.

Human Biochemistry. 2nd Ed. By ISRAEL S. KLEINER, Ph.D., Professor of Biochemistry and Director of the Department of Physiology and Biochemistry, New York Medical College, New York. 649 pages; 17 × 25 cm. C. V. Mosby Co., St. Louis. 1948. Price, $7.00.

Dr. Kleiner's book was written primarily for medical students and physicians who wish to familiarize themselves with those aspects of biochemistry which pertain to the human body. It attempts to present "clinical aspects of biochemistry without usurping any clinicians' domain and without neglecting the fundamentals" of the subject. The program is an ambitious one covering as it does the basic chemistry of carbohydrates, lipids, proteins, enzymes, vitamins, hormones, as well as metabolism in its varied aspects. The book will serve the student both in his courses in biochemistry and physiology and later in his period of clinical training. The practicing physicians will find it valuable as a reference text.

E. G. S.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Pediatrics—Volume IV. Editorial Board: S. Z. LEVINE, Cornell University Medical College, New York; ALLAN M. BUTLER, Harvard Medical School, Boston; L. EMMETT HOLT, JR., New York University, College of Medicine, New York, and A. ASHLEY WEECH, University of Cincinnati, College of Medicine, Cincinnati. 316 pages; 24 × 15.5 cm. 1949. Interscience Publishers, Inc., New York. Price, $6.50.

Arterial Hypertension: Its Diagnosis and Treatment. 2nd ed. By IRVINE H. PAGE, M.D., and ARTHUR CURTIS CORCORAN, M.D., Research Division of the Cleveland Clinic Foundation, Cleveland. 400 pages; 21 × 14.5 cm. 1949. The Year Book Publishers, Inc., Chicago. Price, $5.75.

Bone and Joint Radiology. By EMERIK MARKOVITS, M.D., Formerly Scientific Collaborator of the Central Radiologic Institute of the General Hospital (Holzknecht-Institute), Vienna, etc. 446 pages; 26 × 18 cm. 1949. The Macmillan Company, New York. Price, $20.00.

Clinical Diagnosis by Laboratory Examinations. 2nd ed. By JOHN A. KOLMER, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry of Temple University, etc. 1212 pages; 25.5 × 17 cm. 1949. Appleton-Century-Crofts, Inc., New York. Price, $12.00.

The Development of Gynaecological Surgery and Instruments: A Comprehensive Review of the Evolution of Surgery and Surgical Instruments for the Treatment of Female Diseases from the Hippocratic Age to the Antiseptic Period. By JAMES V. RICCI, M.D., Clinical Professor of Gynaecology and Obstetrics, New York Medical College, etc. 594 pages; 27 × 18.5 cm. 1949. The Blakiston Company, Philadelphia. Price, $12.00.

Differential Diagnosis of Chest Diseases. By JACOB JESSE SINGER, M.D., F.A.C.P., F.C.C.P., Medical Director of the Rose Lampert Graff Foundation, Beverly Hills, etc. 344 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, $7.50.

Digitalis and Other Cardiotonic Drugs. 2nd ed. By ELI RODIN MOVITT, M.D., Chief of Medicine, Veterans Administration Hospital, Oakland, California, etc. 245 pages; 24.5 × 16 cm. 1949. Oxford University Press, New York. Price, $5.75.

Diseases of the Aorta: Diagnosis and Treatment. By NATHANIEL E. REICH, M.D., F.A.C.P., Associate in Medicine, Long Island College of Medicine, etc. 288 pages; 24 × 16 cm. 1949. The Macmillan Company, New York. Price, $7.50.

Die Dystrophie. By PROFESSOR DR. MED. HEINRICH BERNING. 197 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, Halbleinen DM 18.—

Functional Localization in Relation to Frontal Lobotomy, Being the William Withering Memorial Lectures Delivered at the Birmingham Medical School, 1948. By JOHN F. FULTON, O.B.E., M.D., D.SC., LL.D. (Birm.). 140 pages; 21 × 13 cm. 1949. Oxford University Press, New York. Price, $3.00.

Golden Jubilee World Tribute to Dr. Sidney V. Haas, In Honor of His Pioneering Contribution to Celiac Therapy and the Treatment of the Hypertonic Infant, and of the Completion of His Fiftieth Year of Medical Practice. 38 pages; 24 × 15.5 cm. 1949. The Committee for the Golden Jubilee Tribute to Dr. Sidney V. Haas, New York.

Grundlagen der Funktionellen Urologischen Röntgendiagnostik. By DR. MED. HABIL. WALTER PFEIFER. 88 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart. Price, kart DM 9.60.

Histopathology of the Skin. By WALTER F. LEVER, M.D., Instructor in Dermatology, Harvard Medical School, etc. 449 pages; 24 × 15.5 cm. 1949. J. B. Lippincott Company, Philadelphia. Price, $10.00.

Human Pathology. 7th ed. By HOWARD T. KARSNER, M.D., LL.D., Former Professor of Pathology, Western Reserve University, etc. 927 pages; 26 × 18 cm. 1949. J. B. Lippincott Company, Philadelphia. Price, $12.00.

Jest What the Doctor Ordered. By DR. FRANCIS LEO GOLDEN; with a Foreword by N. BERTRAM COLE, M.D., F.A.C.S. 256 pages; 21 × 14 cm. 1949. Frederick Fell, Inc., New York. Price, $2.95.

Malaria: The Biography of a Killer. By LEON J. WARSHAW, M.D. 348 pages; 22 × 14.5 cm. 1949. Rinehart & Company, Inc., New York. Price, $3.75.

Minutes of the Seventh Streptomycin Conference, Held on April 21, 22, 23, & 24, 1949, Cosmopolitan Hotel, Denver, Colorado. Prepared and Edited by Veterans Administration, Area Office, Washington, D. C. 360 pages; 26 × 20 cm. (paper-bound). 1949. Veterans Administration, Washington, D. C. Price, Not for sale—limited edition for distribution to VA hospitals and medical libraries.

Neoplasms of the Dog. By R. M. MULLIGAN, M.D., Professor of Pathology in the University of Colorado Medical Center School of Medicine. 135 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $4.00.

Textbook of Bacteriology (Eleventh Edition of Muir & Ritchie's "Manual"). By C. H. BROWNING, M.D., LL.D., D.P.H., F.R.S., Gardiner Professor of Bacteriology, University of Glasgow, and T. J. MACKIE, C.B.E., M.D., LL.D., D.P.H., Professor of Bacteriology, University of Edinburgh. 907 pages; 25.5 × 16 cm. 1949. Oxford University Press, New York. Price, $12.75.

A Textbook of Medicine for Nurses. 5th ed. By E. NOBLE CHAMBERLAIN, M.D., M.SC., F.R.C.P., Senior Lecturer in Medicine, University of Liverpool, etc.; with a Foreword by DAME ELLEN MUSSON, D.B.E., R.R.C., LL.D., Formerly Chairman, General Nursing Council for England and Wales. 491 page; 22.5 × 14 cm. 1949. Oxford University Press, New York. Price, $6.00.

Unipolar Lead Electrocardiography, Including Standard Leads, Augmented Unipolar Extremity Leads and Multiple Unipolar Precordial Leads, and a Section on Cardiac Arrhythmias. 2nd ed. By EMANUEL GOLDBERGER, B.S., M.D., Adjunct Physician, Montefiore Hospital, New York. 392 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, $7.50.

COLLEGE NEWS NOTES

Elections to Fellowship and Associateship

American College of Physicians

November 13, 1949

(FELLOWS, FULL CAPITALS: Associates, lower case)

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Albert Heyman ..... Atlanta, Ga.
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GLENN IVAN HILLER ..... Highland Park, Mich.
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Irving Nathan Holtzman ..... Brooklyn, N. Y.
Ralph E. Homann, Jr. ..... Los Angeles, Calif.

John Williams Hooker ..... Wilmington, Del.
Harry Aloysius Horstman, Jr. ..... M. C., U. S. Army
Dorothy Millicent Horstmann ..... New Haven, Conn.
Harvey Horwitz ..... Chicago, Ill.
John Wade Howard ..... Wilmington, Del.
KYRAN EMMETT HYNES ..... Seattle, Wash.

Lucien Waterman Ide ..... St. Joseph, Mo.
Irving Innerfield ..... Nyack, N. Y.

Albert Jackson ..... Wadsworth, Kans. (V.A.)
Alvah Rudolph Jenkins ..... Englewood, N. J.
Herbert William Jenkins ..... Sacramento, Calif.
ARTELL EGBERT JOHNSON ..... New York, N. Y.
C(ARL) HAROLD JOHNSON ..... Gettysburg, Pa.
Corbet Stephens Johnson ..... Waverly, N. Y.
Arthur Harvey Joistad, Jr. ..... Muskegon, Mich.
GRANVILLE LILLARD JONES ..... Williamsburg, Va.
Theodore Reid Jones ..... Kansas City, Mo.
Carl John Josephson ..... Denver, Colo.

Alfred Kahn, Jr. ..... Little Rock, Ark.
Frank Kaminsky ..... Brooklyn, N. Y.
Walter Fred Kammer ..... Muncie, Ind.
Irving Joseph Kane ..... New York, N. Y.
ROBERT MANOAH KARK ..... Oak Park, Ill.
Bernard Leon Kartin ..... New Haven, Conn.
SOL KATZ ..... Washington, D. C.
PAUL KAUFMAN ..... New York, N. Y.
Ernest Ellsworth Keet, Jr. ..... Queens Village, N. Y.
William Hilliary Keffer ..... Reading, Pa.
William Ernest Kelley ..... Omaha, Nebr.
William Roland Kennedy ..... Montreal, Que., Can.
Morley Job Kert ..... Los Angeles, Calif.
Harry Kessler ..... New York, N. Y. (V.A.)
John Harvey Killough ..... M. C., U. S. Navy
ROBERT COOKE KIMBROUGH, JR. ..... Knoxville, Tenn.
John Anthony Kinczel ..... Trenton, N. J.
Herbert Arthur King ..... Durham, N. C.
Stuart Dawson King ..... North Hollywood, Calif.
Dunham Kirkham ..... Togus, Maine (V.A.)
GERALD KLATSKIN ..... New Haven, Conn.
ARTHUR KLEIN ..... Richmond, Va.
Leon Arthur Kochman ..... Baltimore, Md.
HAROLD WILLIS KOHL ..... Tucson, Ariz.
Abraham Kolodin ..... Bloomfield, N. J.
ROY RACHFORD KRACKE ..... Birmingham, Ala.
Harold Maurice Kramer ..... Louisville, Ky.
Jackson Edmund Kress ..... Missoula, Mont.
William Charles Kuzell ..... San Francisco, Calif.

THOMAS HARRISON LAMBERT ..... La Jolla, Calif.
RICHARD LANGENDORF ..... Chicago, Ill.
ANTHONY JOSEPH LANZA ..... New York, N. Y.
Maurice Kamm Lawrence ..... Swampscott, Mass.
Edgar Athaleston Lawrence ..... New York, N. Y.

David Lehr ..... New York, N. Y.
Stephen Howard Leslie ..... New York, N. Y.
Eli Allen Leven ..... Rochester, N. Y.
Herbert Melville Levenson ..... Framingham, Mass.
Matthew Levine ..... New York, N. Y.
Samuel Marrel Levit ..... Philadelphia, Pa.
William Likoff ..... Philadelphia, Pa.
JOSEPH FRANCIS LINSMAN ..... Beverly Hills, Calif.
EMANUEL WILLIAM LIPSCHUTZ ..... Brooklyn, N. Y.
Lester Lipson ..... Monticello, N. Y.
Jesse Cone Lockhart ..... Peoria, Ill.
HARRY JOSEPH LOWEN ..... New York, N. Y.
John Morgan Lyon ..... Englewood, Colo.

WILLIAM CHARLES MACDONALD ..... St. Louis, Mo.
Thomas Keith MacLean ..... Vancouver, B. C., Can.
Harold Haze Macumber ..... Chichasha, Okla.
Frank Joseph Manganaro ..... Kirkwood, Mo.
Sydney Gerald Margolin ..... New York, N. Y.
Jerome David Markham ..... Richmond, Va.
THOMAS WILLIAM MATTINGLY ..... M. C., U. S. Army
EDWARD MATZGER ..... San Francisco, Calif.
Edward Schuyler McCabe ..... Philadelphia, Pa.
Marcus Denney McDivitt ..... Pittsburgh, Pa.
Douglas Francis McDowell ..... Santa Barbara, Calif.
Charles Joseph McGee ..... Brockton, Mass.
FRANK BARTLETT McGLONE ..... Denver, Colo.
Arthur Joseph McSteen ..... Greensburg, Pa.
Edward Idel Melich ..... Largo, Fla. (V.A.)
Patterson Morris Menlowe ..... McKeesport, Pa.
Arthur Jesse Merrill ..... Atlanta, Ga.
John Putnam Merrill ..... Waban, Mass.
William Josef Messinger ..... New York, N. Y.
John Wright Middleton ..... Galveston, Tex.
Ernest Boyd Millard, Jr. ..... Rochester, N. Y.
Solomon Samuel Mintz ..... Philadelphia, Pa.
HOWARD SCOTT MITCHELL ..... Montreal, Que., Can.
Frank Corbin Moister ..... Hanover, N. H.
ROLLEN WAYNE MOODY ..... Denver, Colo.
J(oseph) Lloyd Morrow ..... Passaic, N. J.
Paul Vanderhoff Morton ..... San Jose, Calif.
Jack Duane Myers ..... Durham, N. C.
SAMUEL MYERSON ..... Bay Pines, Fla. (V.A.)

Max J. Nareff ..... Jamaica, N. Y.
Maurice Nataro ..... Louisville, Ky. (V.A.)
John Robert Neefe ..... Philadelphia, Pa.
Jack Nelson ..... New York, N. Y.
JAMES DAVID NELSON ..... Spartanburg, S. C.
Carl Robert Newman ..... Redwood City, Calif.
Robert H. Nickau ..... Jacksonville, Fla.
Joseph Henry Nicholson ..... Lawrence, Mass.

Joseph Mazarin Oppenheim ..... Detroit, Mich.
James Archer Orbison ..... M. C., U. S. Army

Norman Williston Osher ..... Milwaukee, Wis.

Henry Stoddert Parker ..... M. C., U. S. Army
John Lawrence Parnell ..... Vancouver, B. C., Can.
Arpad Pauncz ..... Lyons, N. J. (V.A.)
John Strother Pearson ..... Huntington, W. Va.
SIDNEY LINCOLN PENNER ..... Stratford, Conn.
Arnold Zachary Pfeffer ..... New York, N. Y.
Robert Toms Pigford ..... Wilmington, N. C.
FRANK P. PIGNATARO ..... Red Bank, N. J.
Howard Freeman Polley ..... Rochester, Minn.
Eduardo R. Pons, Jr. ..... Santurce, P. R.
Rolf Falk Poser ..... Columbus, Wis.
F(RANK) KENNETH POWER ..... Salem, Ore.
John Alan Prior ..... Columbus, Ohio
Fellowes Morgan Pruyn ..... Mount Kisco, N. Y.

Gordon Woodrow Raleigh ..... Evanston, Ill.
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Sanford MacArthur Rathbun ..... Beatrice, Nebr.
WALTER REDISCH ..... Jackson Heights, N. Y.
Samuel Boswell Reich ..... Hackensack, N. J.
GEORGE HENRY REIFENSTEIN ..... Syracuse, N. Y.
NORMAN REITMAN ..... New Brunswick, N. J.
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Allen David Riemer ..... Denver, Colo.
William Henry Riser, Jr. ..... Birmingham, Ala.
DANIEL CHRISTOPHER RIVERS ..... Cincinnati, Ohio
Milton Herbert Robbins ..... New York, N. Y.
HOBART ROGERS ..... Oakland, Calif.
Harry Evan Rollings ..... Savannah, Ga.
Alvin Abe Rosenberg ..... Morristown, N. J.
Homer Rosenberger, Jr. ..... Whittier, Calif.
HAROLD ROSENBLUM ..... San Francisco, Calif.
JACOB ALVIN ROSENKRANTZ ..... Mount Vernon, N. Y. (V.A.)
HENRY CARL ROSENSTIEL ..... Albuquerque, N. M. (V.A.)
John Bruce Ross ..... Washington, D. C.
JOSEPH FOSTER ROSS ..... Brookline, Mass.
Ralph Dinsmore Ross ..... M. C., U. S. Navy
Harold Philmore Roth ..... Shaker Heights, Ohio (V.A.)
Oscar Roth ..... New Haven, Conn.
SAUL DAVID ROTTER ..... West Palm Beach, Fla.
John Henry Rowland ..... New Brunswick, N. J.
Sidney Rubin ..... Topeka, Kans. (V.A.)
Wayne Rundles ..... Durham, N. C.

S(amuel) Senior Sack ..... Flushing, N. Y.
W(oodrow) Wilson Schier ..... Boston, Mass.
Burton Lewis Schmier ..... Detroit, Mich.
Adolph Benedict Schneider, Jr. ..... Cleveland, Ohio
Joseph Henry Schwab ..... Woodhaven, N. Y.
Joseph Atlas Schwartz ..... Atlanta, Ga. (V.A.)
Wirt Stanley Scott, Jr. ..... Stockton, Calif.
ISIDOR SILBERMANN ..... New York, N. Y.
Charles Silverberg ..... St. Louis, Mo.

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Maurice Snyder ..... Salina, Kans.
Arnold Stanton ..... Richmond Hill, N. Y.
Louis Wells Staudt ..... Ann Arbor, Mich.
James Milton Steele ..... Jamestown, N. Y.
LAWRENCE IRVING STELLAR ..... Newton Center, Mass.
Edward Amberg Stern ..... Rochester, N. Y.
Marvin Stern ..... Brooklyn, N. Y.
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Chester Pratt Stevenson ..... Fort Logan, Colo. (V.A.)
Herman Hull Stone ..... Oklahoma City, Okla. (V.A.)
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Lee Stover ..... Lincoln, Nebr.
Arnold Ferdinand Strauss ..... Norfolk, Va.
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Henry Harding Tift ..... Macon, Ga.
Philip Murry Tiller, Jr. ..... New Orleans, La.
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David Turnoff ..... Philadelphia, Pa.

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Paul Anton Van Pernis ..... Grand Rapids, Mich.
Helen D. Van Vactor ..... Indianapolis, Ind.
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Cristobal Alberto Vicens ..... New York, N. Y.

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Paul Weitz ..... Lyons, N. J. (V.A.)
William Charles Wermuth ..... Philadelphia, Pa.
Abraham Werner ..... New York, N. Y. (V.A.)
JOHN OVENSTONE WESTWATER ..... Los Angeles, Calif.
Frederick Edward Wetzel ..... M. C., U. S. Navy
Benjamin Morrill Wheeler ..... Edmonton, Alta., Can.
CLARENCE BERNARD WHIMS ..... Atlantic City, N. J.
RANDALL ALLEN WHINNERY ..... Detroit, Mich.
Harold Nelson Willard ..... Claverack, N. Y.
Aubrey Howard Williams ..... Fort Wayne, Ind.
Conger Williams ..... Milton, Mass.
George Ralph Williamson ..... Pittsburgh, Pa.
REX HAMILTON WILSON ..... Akron, Ohio
Thomas Barnette Wilson ..... Raleigh, N. C.
IRVING WOLFE WINIK ..... Washington, D. C.
Henry John Winsauer ..... Sheboygan, Wis.
CHARLES WILMER WIRTS ..... Philadelphia, Pa.
A(lbert) Walter Wise ..... Rock Island, Ill.
Charles Parker Wofford ..... Johnson City, Tenn.
George Anthony Wolf, Jr. ..... New York, N. Y.
RALPH WOLPAW ..... Cleveland, Ohio
John Howard Woodbridge ..... San Luis Obispo, Calif.
Thomas Clarkson Worth ..... Raleigh, N. C.
Myron Wright ..... New York, N. Y.
J(ohn) Lanier Wyatt ..... Nashville, Tenn.
CARL IGLAUER WYLER ..... Cincinnati, Ohio

Hyman Joseph Zimmerman ..... Washington, D. C.
Joseph J. Zimmerman ..... Philadelphia, Pa.
Cecil M. Zukerman ..... Davenport, Iowa

31st Annual Session

The American College of Physicians

The Consulting Committee on Annual Sessions met with President Reginald Fitz, General Chairman Chester S. Keefer, and other representatives of the Boston Committees, on November 12, in connection with the program and arrangements for the 31st Annual Session of the College at Boston, April 17–21, 1950. With the exception of one series of panel discussions and certain hospital clinics, the scientific programs will all be conducted in Mechanics' Hall on Huntington Avenue. Several innovations, including color televised clinics, are being planned. The program of General Sessions and Morning Lectures arranged by President Fitz, and the program of Clinics and Panel Discussions, as well as entertainment features, planned by General Chairman Keefer and his local committees are fast nearing completion. A feature of entertainment will be a concert by the Boston Symphony Orchestra on Monday evening, April 17.

A Housing Bureau has been set up in connection with the Boston Convention Bureau, 80 Federal Street, Boston 10, Mass., through which all hotel reservations shall be made, except in the case of speakers on the program, Officers, Regents and Governors of the College, whose accommodations will be engaged by the Executive Secretary. An adequate number of rooms is available. A number of the functions, such as the Convocation and Annual Banquet, will be held at the Statler Hotel. Some series of the Panel Discussions will be held at the Copley Plaza Hotel. Reservation

forms for rooms will be distributed to all members with the program on or about February 1.

Admission of Non-Members to the Boston Meeting

Due to excessively crowded conditions the past two years, partially occasioned by the large number of non-sponsored non-members, and at the urgent demand of members of the College, the attendance of non-members at the Boston Session will be limited to those who are specifically sponsored by letter by members of the College. Such non-members should be sponsored three weeks in advance of the Session through letters to the Executive Office of the College, 4200 Pine Street, Philadelphia 4, Pa. The non-member registration fee, which not only covers admission to the Meeting but entitles the attendant to the proceedings as published in the ANNALS OF INTERNAL MEDICINE, will be $25.00.

Candidates for Membership

The American College of Physicians

Meetings of the Committee on Credentials will be held March 19 and April 15, 1950. Provisions of the By-Laws require that proposals of candidates shall be filed in the Executive Office at least 60 days in advance of action.

Proposed Graduate Courses

The Advisory Committee on Postgraduate Courses, with the approval of the Board of Regents, has presented the following tentative schedule of courses for the future. It must be understood that the directors and the institutions must be consulted before final announcements may be made. Furthermore, dates will be announced a little later. It is proposed to publish the Postgraduate Bulletin for the Spring of 1950 at an early date.

Spring, 1950, Proposed Courses:

Internal Medicine: University of California School of Medicine, San Francisco; one week; to be scheduled just before the annual meeting of the American Medical Association in June, 1950.

Clinical Allergy: Roosevelt Hospital, New York, N. Y.; one week.

Diseases of the Circulation: Michael Reese Hospital, Chicago, Ill.; one week.

Electrocardiography: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M. D., Director; one week.

Endocrinology: University of Illinois et al., Chicago, Ill., Willard O. Thompson, M.D., F.A.C.P., Director; one week.

Diseases of the Blood Vessels: Cornell University Medical College, New York, N. Y.; one week.

Physiological Basis of Psychosomatic Medicine: Neurological Institute, New York, N. Y.; one week.

Summer, 1950, Proposed Course:

Clinical Aspects of Malnutrition: Hospital de Enfermedades de la Nutricion, Mexico, D. F.; Salvador Zubiran, M.D., F.A.C.P., Director; two weeks, August 14–26, 1950.

Autumn, 1950 Proposed Courses:

Hematology: Boston, Mass.; William B. Castle, M.D., F.A.C.P., Director; one week.

Internal Medicine: University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; one week.

GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week.

INTERNAL MEDICINE: University of Utah School of Medicine, Salt Lake City, Utah; one week.

1951 Suggested Courses:

INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY: University of Cincinnati College of Medicine, Cincinnati, Ohio; M. A. Blankenhorn, M.D., F.A.C.P., Director; one week.

PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE: University of Toronto Faculty of Medicine, Toronto, Ont.; Ray F. Farquharson, M.D., F.A.C.P., Director; one week.

INTERNAL MEDICINE: University of Oregon Medical School, Portland, Ore.; Howard P. Lewis, M.D., F.A.C.P., Director; one week.

ELECTROCARDIOGRAPHY: Emory University School of Medicine, Atlanta, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director; one week.

LATIN-AMERICAN FELLOWSHIP PROGRAM

The American College of Physicians has announced, in the July, 1949 issue of this journal, its Latin-American Fellowship Plan in coöperation with the W. K. Kellogg Foundation. Outstanding young physicians will be nominated to the College and Foundation by local committees in Latin-American countries and those to whom fellowships are awarded will be brought to the United States or Canada for a year or more of special training. Designed to stimulate progress in the teaching of internal medicine and research, and to help the most promising young doctors of medicine in the Latin-American countries to prepare for teaching and research careers in their native countries, the program also will serve to increase understanding among the American republics by serving as a medium for the exchange of knowledge and acquaintanceships.

At a meeting of the Committee on Fellowships and Awards on July 30, 1949, the initial three Fellows were selected and were placed in an orientation course at Cornell University Medical College for a period of six months, following which they will be assigned to specific preceptors for a period of one year. These three include: Dr. Henrique BENAIM Pinto, Caracas, Venezuela; Dr. Rudolfo DE CASTRO Curti, Mexico, D. F.; and Dr. Horacio JINICH Brook, Mexico, D. F.

Additional awards approved, to start in 1950, were made to the following: Dr. Fructuoso BIEL Cascante, Concepcion, Chile; Dr. Roberto Figueria SANTOS, Salvador, Brazil; Dr. Egon LICHTENBERGER Salomon, Bogota, Colombia; and Dr. Francisco VON LICHTENBERG Schneider, Mexico, D. F.

Dr. Benjamin G. Horning, Director of the Medical Division of the Kellogg Foundation, is responsible for the visitation and investigation of candidates in the Latin-American countries. The Committee on Fellowships and Awards of the American College of Physicians is officially responsible for the selection of the Fellows, the supervision of their program and the placing of them under a preceptor. Funds for the operation of the program are provided by the Kellogg Foundation.

RESEARCH FELLOWSHIPS OF THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians awards a limited number of Fellowships in Medicine for the customary period of one year, beginning July 1 of each year. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their

preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend varies from $2,200 to $3,200, according to the obligations of the recipient. Application forms are obtainable through the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

Applications may be filed for the period July 1, 1951–June 30, 1952. All Fellowships for 1950–51 have been assigned.

In accordance with the recommendations of the Committee on Fellowships and Awards, the Board of Regents on November 13, 1949, made the following awards of Research Fellowships to start July 1, 1950:

Edward Harvey Estes, Jr., M.D.; aged 24; a graduate of Emory University School of Medicine, 1947; to work under Dr. James V. Warren, Department of Physiology, Emory University School of Medicine, on the response of the pulmonary vascular bed to hemodynamic alterations in the systemic circuit.

Dalton Jenkins, M.D.; aged 31; a graduate of the University of Colorado School of Medicine, 1943; to work under Dr. George W. Thorn, F.A.C.P., Peter Bent Brigham Hospital, Boston, Mass., on a study of the adrenal hormones on specific metabolic functions, with particular relationship to muscle metabolism.

Edward Howell Lanphier, M.D.; aged 27; a graduate of the University of Illinois College of Medicine, 1949; to work under Dr. Julius H. Comroe, Jr., F.A.C.P., Department of Physiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., on the investigation of new functional tests of the cardiovascular-pulmonary system.

William Andrew MacIlwaine, M.D.; aged 27; a graduate of the University of Virginia Department of Medicine, 1947; to work under Dr. Byrd S. Leavell, F.A.C.P., University of Virginia Department of Medicine, Charlottesville, Va., to study the effects of various procedures and substances on hemoglobin metabolism in sickle cell anemia.

Cheves McCord Smythe, M.D.; aged 25; a graduate of Harvard Medical School, 1947; to work under Dr. Stanley E. Bradley, Department of Medicine, Presbyterian Hospital, New York, N. Y., on a problem concerned with renal and hepatic physiology as studied by blood flow technics.

William Jape Taylor, M.D.; aged 25; a graduate of Harvard Medical School, 1947; to work under Dr. J. D. Myers, Department of Medicine, Duke University School of Medicine, Durham, N. C., to study the effects of insulin, epinephrine and adrenal cortical substances on the splanchnic glucose, phosphate and potassium intakes and outputs; also to study the effect of parenteral fat on hepatic blood flow and oxygen consumption.

Dr. Edward Harvey Estes, Jr. was selected from the above group of six to be designated as the "Alfred Stengel Research Fellow."

Mississippi Regional Meeting Report

The second Annual ACP Regional Meeting of the State of Mississippi was held at Jackson, Miss., October 8, 1949, under the Governorship of Dr. John G. Archer, F.A.C.P., of Greenville. Every feature of the program and of the meeting was eminently successful, as attested to by the fact that every member of the College from Mississippi with the exception of four was present. There were 7 members of the College from Tennessee, 3 from Arkansas, and 1 from Louisiana, and among the guests were Dr. William C. Chaney, F.A.C.P., Governor for Tennessee, Dr. A. A. Blair, F.A.C.P., Governor for Arkansas, and Dr. G. W. F. Rembert, F.A.C.P., former Governor for Mississippi. At the reception and banquet in the evening, there were 71 members, guests and wives in attendance, a considerable increase over the attendance at the first Regional Meeting a year ago.

Gift to the College Library

Grateful acknowledgment is made to Dr. Howard A. Rusk, F.A.C.P., New York, N. Y., for an autographed copy of his book, "New Hope for the Handicapped," and for several reprints dealing with rehabilitation and related subjects.

American College of Physicians Activities in Hawaii

Members of the American College of Physicians in Hawaii, under the leadership of Dr. Nils P. Larsen, Governor, have organized a monthly staff meeting at the Tripler General Hospital. The meetings are conducted as panel discussions with members representing different special fields discussing a chosen topic from the points of view of different medical specialties. College members will also undertake to prepare reports based on health surveys conducted in coöperation with the Board of Health. Still a further activity of the members in Hawaii includes a plan for each member to donate $3.00 toward a subscription for the medical section of *Excerpta Medica* for the local medical library which is at present operating on a greatly curtailed budget.

New Books Recently Published by Fellows of the College

Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., has recently edited "The 1948 Yearbook of Pathology and Clinical Pathology," published by the Yearbook Publishers.

Dr. Wilburt C. Davison, F.A.C.P., Professor of Pediatrics at Duke University School of Medicine, Durham, N. C., has recently brought out the 6th Edition of "The Compleat Pediatrician—Practical, Diagnostic, Therapeutic and Preventive Pediatrics," published by the Duke University Press.

Dr. Howard A. Rusk, F.A.C.P., New York, N. Y., "New Hope for the Handicapped: The Rehabilitation of the Disabled from Bed to Job," published by Harper and Brothers.

Dr. Donald C. Young (Associate) and Dr. Alvin F. Coburn, Detroit, Mich., "The Epidemiology of Hemolytic Streptococcus during World War II in the United States Navy," published by Williams and Wilkins Company.

Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., "Obesity," published by Charles C. Thomas.

Dr. Willis M. Fowler, F.A.C.P. and Dr. Elmer L. DeGowin, F.A.C.P., Iowa City, Iowa, second edition of "Hematology for Students and Practitioners," published by Paul B. Hoeber, Inc.

A.C.P. Fellows Appointed Consultants to Medical Service, U. S. Air Force

Major General Malcolm C. Grow, Surgeon General, U. S. Air Force, recently announced the appointments of Consultants to that Service, among whom are the following Fellows of the American College of Physicians: Dr. William P. Holbrook, Tucson, Ariz., and Dr. Phillip T. Knies, Columbus, Ohio, Internal Medicine; Dr. Charles E. Kossman, New York, N. Y., Cardiology; Dr. Howard A. Rusk, New York, N. Y., Physical Medicine.

Projection Equipment Donated by Dr. Leaman

Dr. William G. Leaman, Jr., F.A.C.P., who directed Course No. 7, Cardiovascular Diseases, under the auspices of the American College of Physicians, at Philadelphia, Pa., May 2–7, 1949, and whose group initiated the use of the new auditorium at the College Headquarters, has donated funds to the College for the purchase of a pro-

jector for standard slides, a projector for Kodachrome slides, and a sound-motion picture 16 mm. projector. These projectors have been acquired and are of the finest quality, and are now available for all meetings or other events held at the College Headquarters. The gift was accepted with deep appreciation by the Board of Regents at its meeting on November 13, 1949.

President Fitz Becomes Life Member

Dr. Reginald Fitz, F.A.C.P., President of the American College of Physicians, became a Life Member on November 12, 1949, through a generous subscription to the Endowment Fund. The total life members number 799, of whom 69 are now deceased, leaving a balance of 730.

The Life Membership plan of the American College of Physicians is equitable both to the member and to the College. It affords the member an opportunity of paying his full dues during his productive years and while his income is greatest, and thus avoiding the burden of dues later in life. It, therefore, provides a means for underwriting dues years in advance and of receiving the premium of active membership throughout one's entire life. Members are invited to request the Executive Offices to mail them the folder, "Membership Without Dues," which gives all details.

Coming Examinations, Certifying Boards

(1) The American Board of Internal Medicine. William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 West Main St., Madison, Wis. Written Examination—once yearly, to be given on 3rd Monday of October. Oral Examination—Chicago, Ill., February 8–9–10, 1950; Boston, Mass., April 13–14–15, 1950; San Francisco, Calif., June 21–22, 23, 1950.

The examination in Boston is given during the week just preceding the Annual Session of the American College of Physicians; the examination in San Francisco is given during the week preceding the annual meeting of the American Medical Association.

Oral examinations in the sub-specialties of Allergy, Cardiovascular Disease, Gastro-enterology and Tuberculosis will be held at the same time and places.

The closing dates for acceptance for all examinations will be January 1, 1950.

(2) The American Board of Pediatrics. John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa. Written Examination—under local monitors, Thursday, January 12, 1950 from 2:00 to 4:00 p.m. This is the only written examination scheduled for 1950. Oral Examination—Richmond, Va., February 10–11–12, 1950; Philadelphia, Pa., March 31, April 1–2, 1950; San Francisco, Calif., June 23–24–25, 1950.

National Conference on Cardiovascular Diseases

A National Conference on Cardiovascular Diseases will be held in Washington, D. C., January 18–20, 1950, under the joint sponsorship of the American Heart Association and the National Heart Institute of the U. S. Public Health Service. This will be the first national conference bringing together physicians, scientists, community service leaders, and members of allied professions to formulate a comprehensive program to combat the nation's leading cause of death.

Dr. Paul D. White, F.A.C.P., Chief Medical Adviser to the National Heart Institute, is Chairman of the Steering Committee.

University of California Medical School Announces Postgraduate Courses, 1950

The University of California Medical School, through its Medical Extension, announces courses in various fields in 1950. Among these are the following:

Clinical Science as Applied to General Medicine: One evening session weekly for 20 weeks, January 9–May 22.

Applied Therapeutics: January 20–February 1.

Special Problems in Pediatrics: February 6–10.

Forensic Medicine: February 6–8.

Gastro-Enterology: August 28–30.

Psychiatry and Neurology: Designed as preparation for examinations of the American Board of Psychiatry and Neurology; August 28–November 17.

Evening Symposia in Medicine: Every Monday evening, September 18–December 4.

Emory University School of Medicine and the University of Georgia School of Medicine Receive Federal Grants for Teaching and Research in Cardiology

Emory University School of Medicine, Atlanta, and the University of Georgia School of Medicine, Augusta, are among 85 medical schools and research institutions to which federal grants have been made for research in cardiology, including the search for a "mechanical heart," a mechanism that would replace the heart during operations. The University of Georgia School of Medicine has been allocated $58,000 for construction and equipment and for additional laboratory and animal quarters. $14,000 for teaching funds and $15,120 for research goes to Emory University School of Medicine. These funds will be used to coördinate the study of heart disease. At Emory University, part of the funds will be used for x-ray equipment to take motion pictures of the heart in action.

The nationwide program for attacking heart disease is covered by federal grants totalling $8,614,737.

Additional Federal Grants for Mental Research

Twelve additional federal grants have been made in aid of research in mental and emotional disorders as follows: Massachusetts General Hospital, $26,308, prefrontal lobotomy studies; University of Iowa, $3,915, anxiety and frustration in animal behavior; Illinois Institute of Technology, $9,400, analysis of topical autobiographies of displaced persons; New York State Department of Mental Hygiene, $7,000, statistical studies; New York University College of Medicine, $21,276, childhood schizophrenia; New York University College of Medicine, $3,726, changes in perceptual functions in organic psychoses; Columbia University, $7,344, psychologic factors in amenorrhea; Columbia University, $13,700, psychosomatic aspects of ulcerative colitis; Institute for Juvenile Research, Chicago, $3,900, analysis of psychophysiologic data on hypnosis and on emotional and behavior disorders; Columbia University College of Physicians and Surgeons, $7,128, space-controlled neural lesions; Wayne University, $19,364, cultural and psychiatric factors in mental health of Hutterites, and University of Washington School of Medicine, $16,262, cingulate gyrus of cerebral cortex, functions and connections.

National Institutes of Health, Bethesda, Md., Proposed $40,000,000 Clinical Center

A clinical center, already in course of construction, for the National Institutes of Health at Bethesda, Md., will be a combined hospital and research institution and will have elaborate medical equipment and basic science laboratories together with hospital facilities for five hundred patients. It will be a fourteen story building, air-conditioned, and will cost $40,000,000. It is scheduled to be completed by July, 1952.

An auditorium seating 500 will be equipped with television, and some seats will be specially wired for the hard of hearing. The center will be supervised by Dr. R. E. Dyer, Director of the National Institutes of Health. It is said that the Government already has "colonies" of trainees for the center established throughout the country, who are being recruited and trained for particular types of research. Surgeon General Leonard A. Scheele of the Public Health Service states that this is to be a research center and not an institution in competition with private physicians and private hospitals. It is stated further that there will be intimate collaboration between the center and the medical schools of the country.

Dr. J. Roscoe Miller, F.A.C.P., Becomes 12th President of Northwestern University

On October 26, 1949, Dr. J. Roscoe Miller, F.A.C.P., was installed as 12th President of Northwestern University, and was awarded the honorary degree of doctor of laws. Dr. Miller had been a member of the faculty of Northwestern University for nineteen years and had been Dean of the Medical School since 1941.

Dr. William B. Bean, F.A.C.P., Head of the Department of Internal Medicine at the State University of Iowa College of Medicine, Iowa City, was elected Vice President of the Central Society for Clinical Research, at its recent meeting in Chicago.

Dr. Theodore R. Van Dellen, F.A.C.P., Chicago, Ill., Assistant Professor of Medicine, Northwestern University Medical School, has been appointed Assistant Dean, succeeding Dr. George H. Gardner, resigned.

Dr. Robert F. Pitts, F.A.C.P., Syracuse, N. Y., Professor of Physiology, Syracuse University College of Medicine since 1946, has resigned to become Head of the Department of Physiology and Biophysics and Professor of Physiology at Cornell University Medical College, New York, N. Y., on January 1, 1950. Dr. Pitts was formerly on the faculty at Cornell University. He holds his Ph.D. degree from Johns Hopkins University and his M.D. from New York University. For two years, 1938–40, he was a Fellow of the Rockefeller Foundation.

Dr. George Morris Piersol, M.A.C.P., Secretary-General of the ACP, was a guest on the program of the Puerto Rico Medical Association Meeting at San Juan, December 14–18, 1949.

Dr. Harold G. Wolff, F.A.C.P., Professor of Neurology and Psychiatry, Cornell University Medical College, delivered an address on "Life Situations, Emotions and Bodily Disease" at the New School for Social Research, New York City, on November 4, 1949.

Dr. Paul D. White, F.A.C.P., Boston, Mass., delivered the annual Loevenhart Memorial Lecture, at the University of Wisconsin Medical School, Madison, Wis., November 28. The lecture is sponsored by Phi Delta Epsilon Medical Fraternity.

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., delivered the R. R. Huggins Memorial Lecture of the University of Pittsburgh School of Medicine on November 18, at the Mellon Institute of Pittsburgh. His subject was "Medical Ethics, Democracy and Medical Care." The lecture is sponsored by the Nu Chapter of Phi Delta Epsilon Medical Fraternity.

Dr. James Steele, F.A.C.P., Brooklyn, has been appointed Assistant Professor of Radiological Anatomy and Clinical Assistant Professor of Radiology at the University of South Dakota School of Medical Sciences.

Dr. Paul B. Magnuson, F.A.C.P., Medical Director of the Veterans Administration, in addition to being the Governor of the American College of Physicians, representing the Veterans Administration, is Secretary of the American College of Surgeons.

Dr. James E. Paullin, M.A.C.P., assisted by Dr. C. J. McLoughlin, F.A.C.P., both of Atlanta, is heading the Georgia Diabetes Control Drive, as a part of the national campaign to curb this disease. Support is being given by local health agencies and the Medical Association of Georgia.

Dr. Henry L. Bockus, F.A.C.P., Director of the Department of Internal Medicine and Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, delivered the Julius Friedenwald Memorial Lecture of the University of Maryland, on October 27, his subject being "Acute Pancreatitis."

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170 Board Men in Army Medical Corps

Among the 1,457 Regular Army Officers in the Army Medical Corps as of September 30, 1949, there were 160, or just a shade under 11 per cent, who were certified by American Specialty Boards, according to figures released by the Office of the Surgeon General.

The Army is seeking additional Board men in all of the chief fields, as well as in allergy, cardiology, gastro-enterology, and pulmonary diseases. Under the Graduate Professional Training Program, the Army has residents, in both military and civilian teaching hospitals, in training for Board examinations in almost all the specialties mentioned. Also, under the Civilian Consultants Program, the Surgeon General is availing himself of the services of many civilian specialists, who assist in the teaching of the younger officers, both at home and abroad, and who otherwise contribute their skills toward the accomplishment of the mission of the Army Medical Department.

Higher Pay Approved for Army Physicians

The effect of the recently passed Career Compensation Act of 1949 on the income of medical and dental officers was analyzed today by Major General R. W. Bliss, F.A.C.P., Surgeon General of the Army. He pointed out that a physician who has completed his internship, or a graduate dentist, may be commissioned as a first lieutenant, either in the Regular Army or in the Medical or Dental Corps Reserve, and now receive total pay and emoluments amounting to $473.88 a month (if married or

with dependents), or $458.88 a month (if single and without dependents). These figures compare with former pay totals of $417 and $361, respectively.

A physician or dentist who has acquired sufficient professional experience, and who can meet the other requirements, may be commissioned directly as a captain or higher. A captain's pay, with emoluments, in the Medical and Dental Corps, is now $546 (with dependents) or $531 (without dependents), as against $462 and $426, respectively. On completion of four years of service, a captain receives regular increases at two-year intervals.

Comparable increases have been made in the higher grades, thus making the financial rewards of military service more commensurate with those of private practice.

The Institute for Cancer Research and the Lankenau Hospital Research Institute, Philadelphia, held opening exercises for its new laboratories in Fox Chase on November 16, 1949. There was a program covering a discussion on "Modes of Procedure in Cancer Research," followed by "Open House" and demonstrations by the staffs of the Institutes.

The new laboratories are extensive and represent in facilities and equipment the finest possible setup for cancer research. The staff is being enlarged materially. Both Institutes were organized and have been directed for many years by Dr. Stanley Reimann, F.A.C.P.

The Southern Medical Association held its forty-third Annual Meeting in Cincinnati, Ohio, November 14–17, 1949, under the presidency of Dr. Oscar B. Hunter F.A.C.P., Washington, D. C.

Another Post-Convention Cruise to Bermuda, Following the Boston Session, 1950

Following the Annual Session of the American College of Physicians at New York during the Spring of 1949, an official cruise was conducted to Bermuda, occupying a period of approximately one week. Those of the College who went on the cruise were delighted with all the arrangements and the beauties of the islands. Many were disappointed who could not accompany the group.

The Annual Session in Boston comes at a time, April 17–21, 1950, when there are no appropriate post-convention tours available in the New England states, due to the uncertainty of weather and other factors. Consequently, it has been decided to offer again the cruise to Bermuda. Members can take a late afternoon or evening train from Boston on Friday, April 21, arriving in New York, Saturday morning, where they may spend their morning on personal affairs, and board the "Queen of Bermuda" in the early afternoon. The Itinerary is as follows:

April 22, Sat., 3:00 p.m. Sail from New York; The famous Bays and Skyline, Tea, Dancing in the evening.

23, At sea, the Gulf Stream, Movies, Tea, Dancing.

24, Bermuda, the beautiful islands. Cruise along the charming North Shore and into Hamilton Harbor, one of the loveliest in the world. Arrive Hamilton at 9 a.m.

25, About two and a half days in Bermuda. Opportunity for unusual sightseeing drives, visits to the Caves and Coral Gardens, shopping, golf, or other diversions.

26, Plenty of time today for last minute purchases or drives. Leave Hamilton at 3:00 p.m.

27, Again at sea in the Gulf Stream, Movies, Tea, Dancing.
28, 9:00 a.m. Arrive New York. In most cases members living East of the Mississippi may keep office appointments on Saturday.

The cruise ship will be the luxurious "Queen of Bermuda", especially designed on a world-cruise pattern for the Bermuda run. Every room has a private bath as well as forced ventilation directly under the control of the passengers in each room. The spacious lounges and cafes, swimming pool, ball room, and cozy nooks give the "Queen" the atmosphere of an exclusive club.

The Hotel Princess, a distinguished hostelry in Bermuda, overlooking Hamilton Harbor and the landscaped hills beyond, will be headquarters.

The inclusive price ranges from a minimum of $184.30 up, depending on the type of accommodations demanded.

For full information, plan of the ship, rates, and other data, write direct to Leon V. Arnold, 36 Washington Square West, New York 11, N. Y., who is the conductor of the cruise and who has served the College on previous occasions.

OBITUARIES

DR. THOMAS ADDIS

Thomas Addis, M.D., F.R.C.P., F.A.C.P., San Francisco, Calif., died June 4, 1949, at the age of 67. Dr. Addis was born in Scotland, July 27, 1881. He received the degree of M.B., Ch.B. in 1905, from the University of Edinburgh Faculty of Medicine, and thereafter pursued postgraduate work for two years at Berlin and Heidelberg, Germany. He joined the faculty of Stanford University School of Medicine in 1911, and became Professor of Medicine, serving until 1946, when he retired from active teaching. He was a Fellow of the Royal College of Physicians of Edinburgh and received from that organization, in 1942, the Cullen Prize "for the greatest benefit done to practical medicine in the previous four years." He was a member of the Association of American Physicians, National Academy of Sciences, the American Society for Clinical Investigation, and had been a Fellow of the American College of Physicians since 1930. He was also a diplomate of the American Board of Internal Medicine.

Dr. Addis was a former Carnegie Research Scholar and Fellow, and the first Visiting Fellow at the Long Island College of Medicine, Brooklyn. He had many publications to his credit, among which were "Renal Lesion in Bright's Disease" and "Glomerular Nephritis: Diagnosis and Treatment."

DR. WILLIAM DUNCAN REID

Dr. William Duncan Reid, F.A.C.P., of North Parsonfield, Maine, was a resident of Massachusetts for many years before his retirement. He graduated from Harvard Medical School in 1909 and during World War I served with the American Expeditionary Forces in France. During all the years of his medical life, Dr. Reid was interested in heart disease, and two books appeared under his authorship, "The Heart in Modern Practice" and "Teaching Methods in Medicine." When the first electrocardiograph machine was installed in the Boston City Hospital, Dr. Reid supervised this important department and emphasized the physiological approach to the study and understanding of heart disease. For many years, his interest in the heart during pregnancy commanded his attention and study. All of his friends profited by associating with him, and his students were admiring and loyal.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. BRUCE HUTCHINSON DOUGLAS

Bruce Hutchinson Douglas, A.B., M.D., F.A.C.P., Detroit, Mich., was instantly killed in an automobile accident, en route on a much needed vacation, on August 11, 1949.

Dr. Douglas was born on August 26, 1892. He graduated, A.B., 1915, from Whittier College, and M.D., 1921, from the Rush Medical School. Following graduation he served an internship and residency in the Children's Hospital and in the Herman Kiefer Hospital, Detroit. During 1924–25 he carried on postgraduate studies in preventive medicine and tuberculosis in England, Denmark and Switzerland. Following graduation and residency, Dr. Douglas devoted his life to preventive medicine and to work in the field of tuberculosis. In these fields he became an outstanding authority and teacher. For two years, 1923–25, he was a Lecturer on Tuberculosis to the undergraduate students in the University of Michigan Medical School. Later he became a Lecturer on Tuberculosis in the University of Michigan Postgraduate School of Medicine. For many years he taught preventive medicine and public health in the Wayne University College of Medicine, and in 1941 he became Professor of

Preventive Medicine and Public Health. During the 1930's he served as Medical Director of the Tuberculosis Service at the Herman Kiefer Hospital and Consultant to the William H. Maybury Sanatorium. Later he became Controller of Tuberculosis for the Detroit Department of Health. In 1941 he was elevated to Commissioner of Health in the Detroit Department of Health. In this capacity he served until his unfortunate and untimely death.

Dr. Douglas was a man of great scientific achievements in his field of preventive medicine. He had an amazing capacity for friendship and an ability to get along with his fellow physicians. For this reason the Detroit Department of Health became outstanding throughout the country. Private physicians admired and trusted him. Nowhere else in the country has there been built up such splendid coöperation between the public health service and the private practitioner.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. HILLYER RUDISILL, JR.

Dr. Hillyer Rudisill, Jr., a Fellow of the American College of Physicians for many years, died suddenly of coronary thrombosis at his home on the morning of July 27, 1949.

Dr. Rudisill was born in Macon, Georgia, February 28, 1902. After his undergraduate work at Mercer University, for which he received a B.S. degree, he was graduated from the Jefferson Medical College of Philadelphia in 1924. After visiting hospitals and clinics abroad he interned in New York City and later completed postgraduate work in the field of radiology at the University of Chicago. In 1931 he resigned as Instructor in Roentgenology at the University of Chicago and moved to Charleston, S. C., where he became Professor of Radiology and Radiologist at the Roper Hospital. In 1939 he moved to Atlanta and was Director of the Radiological Department of the Piedmont Hospital, and in 1941 he became Assistant Professor of Radiology at the University of Tennessee College of Medicine and Radiologist to the John Gaston Hospital. He returned to Charleston in 1944, reassuming the duties of Radiologist at the Roper Hospital and continued in this capacity until some months before his death when he attained a long-held ambition and entered the private practice of Radiology. Throughout this time he maintained his teaching connection with the Medical College of South Carolina.

Dr. Rudisill was a member of the Medical Society of South Carolina, of the South Carolina State Medical Association, of the American Roentgen Ray Society, of the American Rheumatism Association, of the Southern Medical Association, and he was a Fellow of the American College of Radiology and of the American College of Physicians. He was also a Diplomate of the American Board of Radiologists.

Dr. Rudisill brought to his chosen field an ingenious and original mind aware both of the possibilities and limitations of radiology. He improvised a device for use in foreign body localization and a probe for seeking metallic particles in subcutaneous tissues. He was the author of a number of scientific publications on both technical and therapeutic subjects, including a manual for x-ray technicians, and contributed to the Official Navy X-Ray Reference Work with a chapter on foreign body localization.

Aside from his professional attainments Dr. Rudisill's interests were wide and varied. He collected a number of items and at one time established an x-ray museum. He was an enthusiastic member of a local Medical History Club and his contributions were always interesting and original. He combined an attractive personality with a keenly analytic mind and an inquisitive nature and was a constant force in compelling both his students and his colleagues to the ultimate in scientific exactitude.

ROBERT WILSON, JR., M.D., F.A.C.P.,
Governor for South Carolina

DR. W. HUARD HARGIS, JR.

Dr. W. Huard Hargis, Jr., died of poliomyelitis on August 15, 1949, in San Antonio, Texas, where he was born on December 27, 1912. Dr. Hargis was a graduate of the University of Texas School of Medicine and received the degrees of B.S. in Medicine and M.D. in 1936. He served an internship at the University of Iowa Hospital in 1936–37, and was a Fellow in Internal Medicine of the Mayo Foundation and received the degree of Master of Science in Medicine in 1942. During World War II, Dr. Hargis was a Major in the Medical Corps of the United States Army.

He was Chief of the Medical Service of the Robert B. Green Memorial Hospital, San Antonio, and Director of the Clinic of the Baptist Memorial Hospital, San Antonio. Dr. Hargis was a Diplomate of the American Board of Internal Medicine and a member of the Bexar County Medical Society, Texas State Medical Association and the American Medical Association. He has been an Associate of the American College of Physicians since 1945. In February of 1948, Dr. Hargis was elected a member of the Texas Club of Internists. He was held in high esteem by his colleagues and a most promising career was closed by his untimely death.

D. W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas

DR. FREDERIC A. ALLING

Dr. Frederic A. Alling died, aged 65, at his home in Montclair, N. J., on October 20, 1949. He had been ill for several months with a malignant hypertension.

He lived a life of intense activity. Always hard working and devoted to his profession, his patients and friends were devoted to him. He became one of the leading and most respected internists in the state.

He was graduated from Princeton in 1907 and from the College of Physicians and Surgeons, Columbia University, in 1911. He interned at the New York Hospital, began practice in Newark, and married Helen, daughter of Bishop Stearley. She and two sons and two daughters survive him.

In World War I Dr. Alling served overseas with the New York Hospital Unit with the rank of Captain. He was an Attending Physician at Newark City Hospital, St. Barnabas Hospital and Presbyterian Hospital, all of Newark. At St. Barnabas he had been President of the Medical Staff. He was Consulting Physician at Rahway and Newark Memorial Hospitals, the Newark Eye and Ear Infirmary, and the Essex Mountain Sanitorium. He was a former president of the Practitioners Society, and had taken an active part in the Essex County and New Jersey State Medical Societies as well as the Academy of Medicine of Northern New Jersey. He was made a Fellow of the College in 1938.

A man of great capacity and many interests, Dr. Alling will be sorely missed by patients, friends, and associates.

George H. Lathrope, M.D., F.A.C.P.,
Governor for New Jersey

DR. JOHN WALTER TORBETT

Dr. J. W. Torbett, F.A.C.P., of Marlin, Texas, died on August 9, 1949, of coronary occlusion.

Dr. Torbett was born July 12, 1871, near Jacksonville, Texas. He was graduated a Bachelor of Science from Centenary College, Lampasas, Texas, in 1891, and received his medical degree from the Atlanta Medical College, Atlanta, Georgia, in 1895, graduating with highest honors. Dr. Torbett practiced continuously in Marlin, Texas, from 1896 until the time of his death. Here he established a clinic and hos-

pital, taking advantage of local mineral waters to create what became a nationally recognized health resort.

Dr. Torbett was a member of the Texas State Medical Association and of the American Medical Association throughout his career. He was Vice-President of the Texas State Medical Association in 1923–24 and 1931–32, and chairman of the Section on Gynecology and Obstetrics in 1919, and chairman of the Section on Radiology and Physical Medicine in 1926. He was president of the Falls County Medical Society in 1947 and also served as president of the Twelfth District Medical Society. He was a diplomate of the American Board of Internal Medicine and of the American Board of Physical Medicine and a life member and a Fellow of the American College of Physicians. He was also a member of the American Congress on Physical Medicine.

Dr. Torbett was a man of unusual talents. He wrote several booklets of poetry and was an accomplished violinist. Philanthropic interests were manifested by scholarships which he established at Southern Methodist University, Dallas, and Southwestern University, Georgetown, Texas, and by many years of public service as a public school trustee, as chairman of the Board of Trustees of the Methodist Orphans' Home of Waco, Texas, and as chairman of the board of stewards of his church.

In 1930 the honorary degree of doctor of laws was conferred upon Dr. Torbett by Southern Methodist University, of which institution he was a founder. His autobiography entitled, "The Doctor's Scrapbook," was published a few years ago.

He was held in high esteem and deep affection by his professional colleagues, patients and many friends.

DAVID W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. WILLIAM HENRY CADE

Dr. William H. Cade of San Antonio, Texas, died July 4, 1949, in San Antonio of coronary occlusion. He was born in San Antonio on November 6, 1892, and received his preliminary education at the University of Texas and was graduated from the University of Texas School of Medicine in May, 1916. From December, 1916, until July, 1917, Dr. Cade practiced in Schertz, Texas. He was a lieutenant in the United States Army from July, 1917, to February, 1919, serving in France. Upon his return from Army service in 1919, Dr. Cade practiced continuously in San Antonio until his death.

Dr. Cade was a member of the Bexar County Medical Society, of which he was president in 1937. He belonged to the State Medical Association of Texas and served as chairman of the Section on Medicine and Diseases of Children in 1936. He was a fellow of the American Medical Association and a member of the International Postgraduate Medical Assembly of Southwest Texas. Of the latter organization he was president in 1935. He was elected a Fellow of the American College of Physicians in 1940. Dr. Cade was a member of staffs of Santa Rosa, Nix and Robert B. Green Hospitals of San Antonio.

He was held in high esteem by his colleagues and patients.

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

ANNALS OF INTERNAL MEDICINE

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ANNALS OF INTERNAL MEDICINE

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Assistant Editor

VOLUME 31
(OLD SERIES, VOLUME XXXV)
July to December, 1949

LANCASTER PRESS, INC., LANCASTER, PA.

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ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital, Baltimore 1, Md.

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2016, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

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